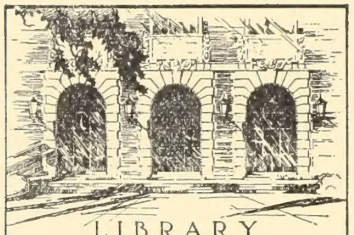

SEMINAR REPORTS

I Semester 1939-40

RANDOM INTERMOLECULAR EXCHANGE OF ORGANIC RADICALS

Calingaert and associates -- Ethyl Gas Corporation

Organic molecules are not dissociated at covalent bonds except by substitution or drastic conditions which change the molecular structure. It has now been found that radicals or atoms can be transferred from one molecule to different molecules in the same class. Thus, an equimolecular mixture of lead ethyl and lead methyl in presence of a catalyst such as CH_3ZnBr, $AlCl_3$, etc., are converted into an equilibrium mixture consisting of $Pb(CH_3)_4$, $Pb(CH_3)_3C_2H_5$, $Pb(CH_3)_2(C_2H_5)_2$, $PbCH_3(C_2H_5)_3$ and $Pb(C_2H_5)_4$. The proportions of these five products are those expected if a random distribution of all R groups between all the lead atoms had taken place. Moreover, experiments showed that this distribution was independent of the R_nM compounds used to form the mixture. During the reaction which was carried out at room temperature, no degradation or loss of product was observed; no heat or other changes could be observed.

In a similar manner, a redistribution reaction was carried out with various mixtures of organic esters. Thus, dimethyl oxalate and diethyl oxalate gave these two products and methyl ethyl oxalate in proportions at equilibrium predicted by random distribution of the alkyl groups. Certain halides interchanged also; a mixture of ethylene bromide and chloride gave these and ethylene chlorobromide.

The authors suggest the necessity for revising the conception of structure of free energy of some covalent bonds.

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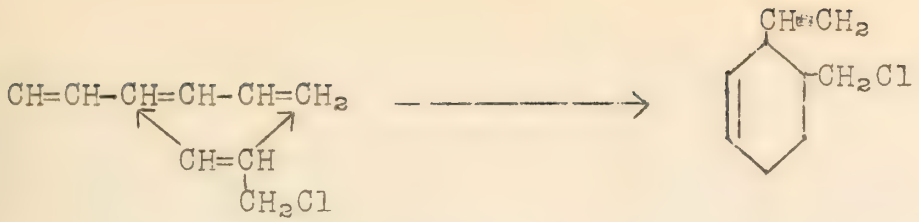
PREPARATION AND POLYMERIZATION OF HEXATRIENE-1,3,5

Kharasch and Sternfeld -- University of Chicago

It has been observed that allyl chloride reacts in liquid ammonia with sodamide to give hexatriene and higher boiling products, most of which are polymers. Thus, sodamide added to allyl chloride gave 30 per cent and the reverse procedure 10 per cent hexatriene.

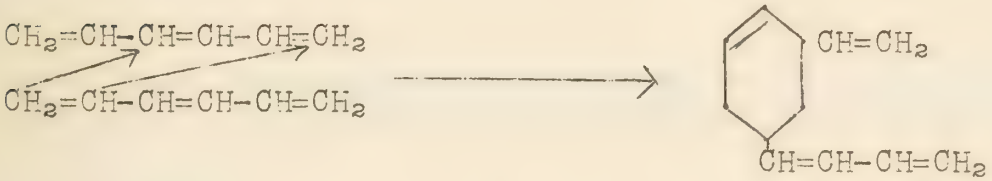
Among the higher boiling substances was obtained a chlorocyclohexene when three moles of allyl chloride and two moles of sodamide reacted.



With excess of sodamide, no halogen derivatives were obtained. The pure fraction in 40 per cent yield gave a molecular weight of 168, added 8 atoms of hydrogen and an index of refraction indicating a ring. Its molecular formula was $C_{12}H_{16}$. Possible structures are shown below.

(1)

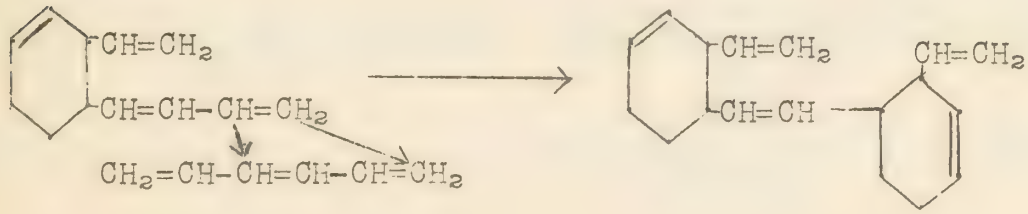
(2)



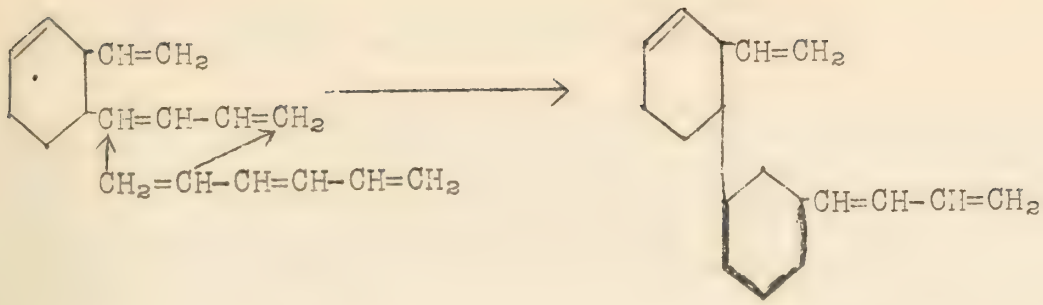
(3)

Since the product adds to maleic anhydride 1 is eliminated. The correct structure was shown to be 2 by reduction to o-ethyl n-butyl cyclohexane which was identified by synthesis in an unambiguous manner.

The next higher fractions in the reaction mixture were a trimer and tetramer obtained by molecular distillation. The structures were postulated as follows.

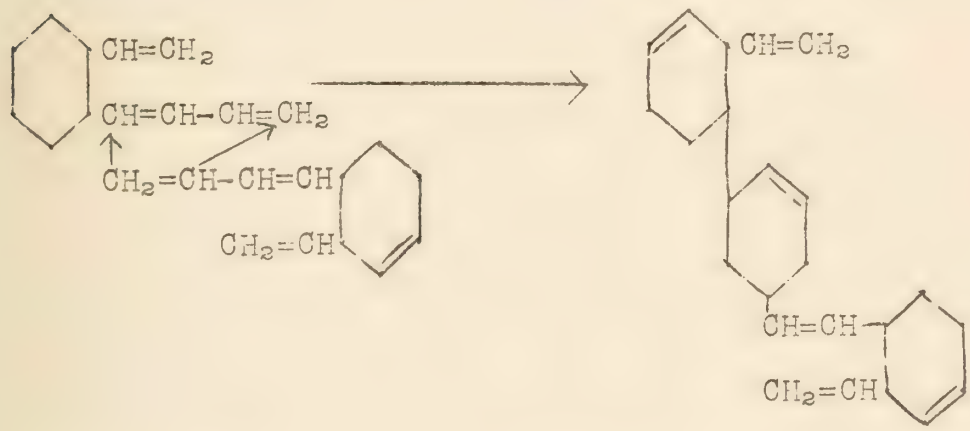


(4)



(5)

Since the product did not react with maleic anhydride, 4 was assumed to be the correct formulation.



(6)

Structure 6 was assigned the tetramer on the basis of no reactivity with maleic anhydride, and the presence of six double bonds.

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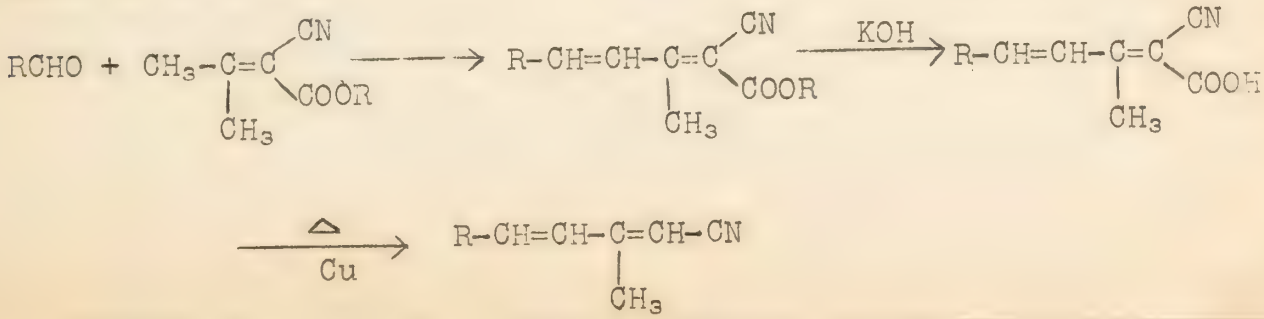
PREPARATION OF POLY-UNSATURATED NITRILES AND ALDEHYDES

Wittig and Hartmann -- University of Freiburg

These authors have been able to prepare polyolefinic nitriles by the following procedure. Piperidine-piperidine acetates was used as catalyst.



Among the specific examples may be mentioned ϕ-$(CH{=}CH)_4CN$ from cinnamic aldehyde and crotylidene cyanacetic ester.

These unsaturated nitriles can be reduced by stannous chloride and hydrogen chloride in ether (Stephen reduction) to the corresponding imide which hydrolyzes to an aldehyde. Wittig has shown that better yields in this step are obtained if stannous bromide and hydrogen bromide are used. Neither reagent is satisfactory for nitriles containing three or more double bonds.

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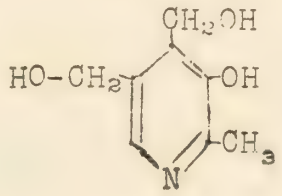
Reported by Roger Adams
September 20, 1939

STRUCTURE AND SYNTHESIS OF VITAMIN B_6

Kuhn -- Kaiser-Wilhelm Institute
Folkers and Keresztesy -- Merck and Company
Rahway, New Jersey

Vitamin B_6 is that factor of the vitamin B complex which prevents or cures a type of dermatitis produced in young rats by a diet in which the only vitamin B components present are purified thiamin and riboflavin. It was discovered by György in 1934 and isolated in the form of its crystalline hydrochloride independently by Keresztesy and Kuhn at about the same time in 1938. It has been given the name "adermin," a term derived from "antidermatitis."

The structure of the vitamin has been shown by Kuhn, and independently by Keresztesy and Folkers, to be:



This structure is supported by the following evidence published by Kuhn:

1. The vitamin has the molecular formula $C_8H_{11}O_3N$, forms a monohydrochloride, and is unaffected by HNO_2. From this evidence a tertiary amine, probably with a ring structure, is deduced.

2. A phenol group is indicated by the color produced with $FeCl_3$ and by the coupling reaction of the compound with diazotized sulfanilic acid. With diazomethane adermin gives a monomethyl ether (II) with the molecular formula $C_9H_{13}O_3N$. This ether gives no phenol reactions.

3. The methyl ether (II) forms a diacetyl derivative which contains no active hydrogen, thus indicating that the three oxygen atoms are in the form of two alcoholic and one phenolic OH groups. Since the methyl ether (II) does not react with lead tetraacetate, the alcoholic hydroxyls do not make up an α-glycol.

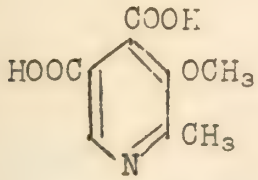
4. Both adermin hydrochloride and the methyl ether (II) yield approximately one molecule of acetic acid upon oxidation with CrO_3-H_2SO_4, thus indicating the presence of one C-methyl group.

5. Absorption spectra and color reactions of adermin indicate that it is a derivative of β-hydroxypyridine.

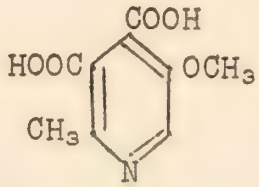
6. The monomethyl ether (II) is oxidized in the cold by neutral $KMnO_4$ to a lactone (III), $C_9H_9O_3N$, and by hot $KMnO_4$ to a tribasic acid (IV), $C_9H_7O_7N$. This acid gives with $FeSO_4$ a blood-red color characteristic of pyridine-α-carboxylic acids. Conversion of the acid to an anhydride (V) results in the loss of CO_2.

The dibasic acid thus obtained (VI) gives no red color with $FeSO_4$ and must, therefore, be 3-methoxypyridine-4,5-dicarboxylic acid. The structure of this compound has been proved by synthesis but the method used has not been reported.

7. Oxidation of the ether (II) with $Ba(MnO_4)_2$ gives a dibasic acid with the methyl group untouched (VII). Since this acid gives no red color with $FeSO_4$, it must not have a carboxyl group in either α-position and adermin must have no $-CH_2OH$ group in an α-position. The formation of the lactone (III) shows that the two $-CH_2OH$ groups are adjacent, and the dibasic acid (VII) must, therefore, have one of the two structures:

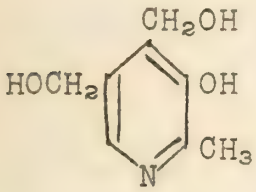


VIIa

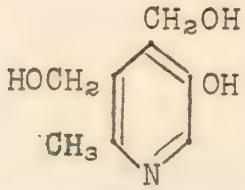


VIIb

8. The above considerations lead to one of the two following structures for adermin:



I

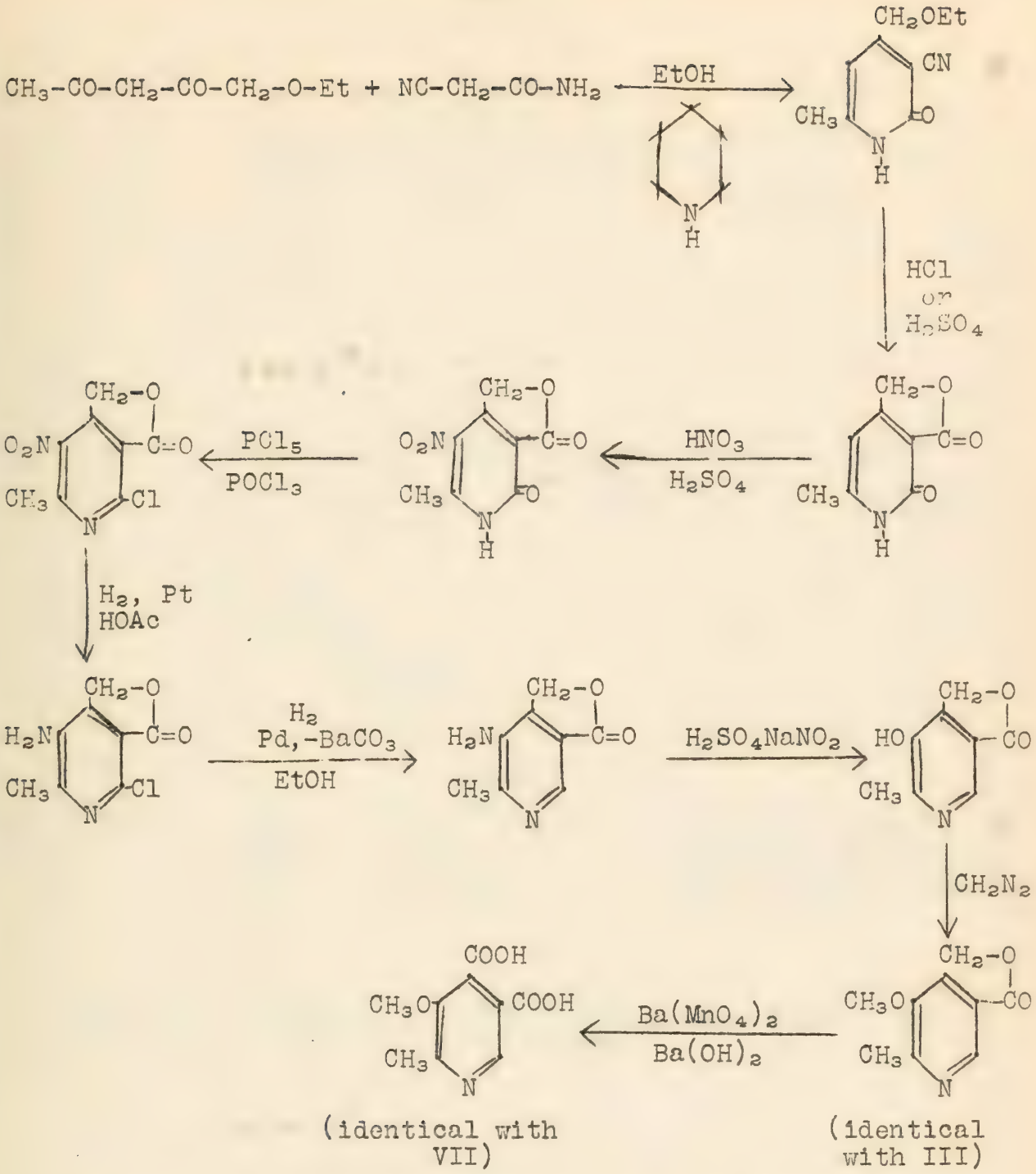


Ia

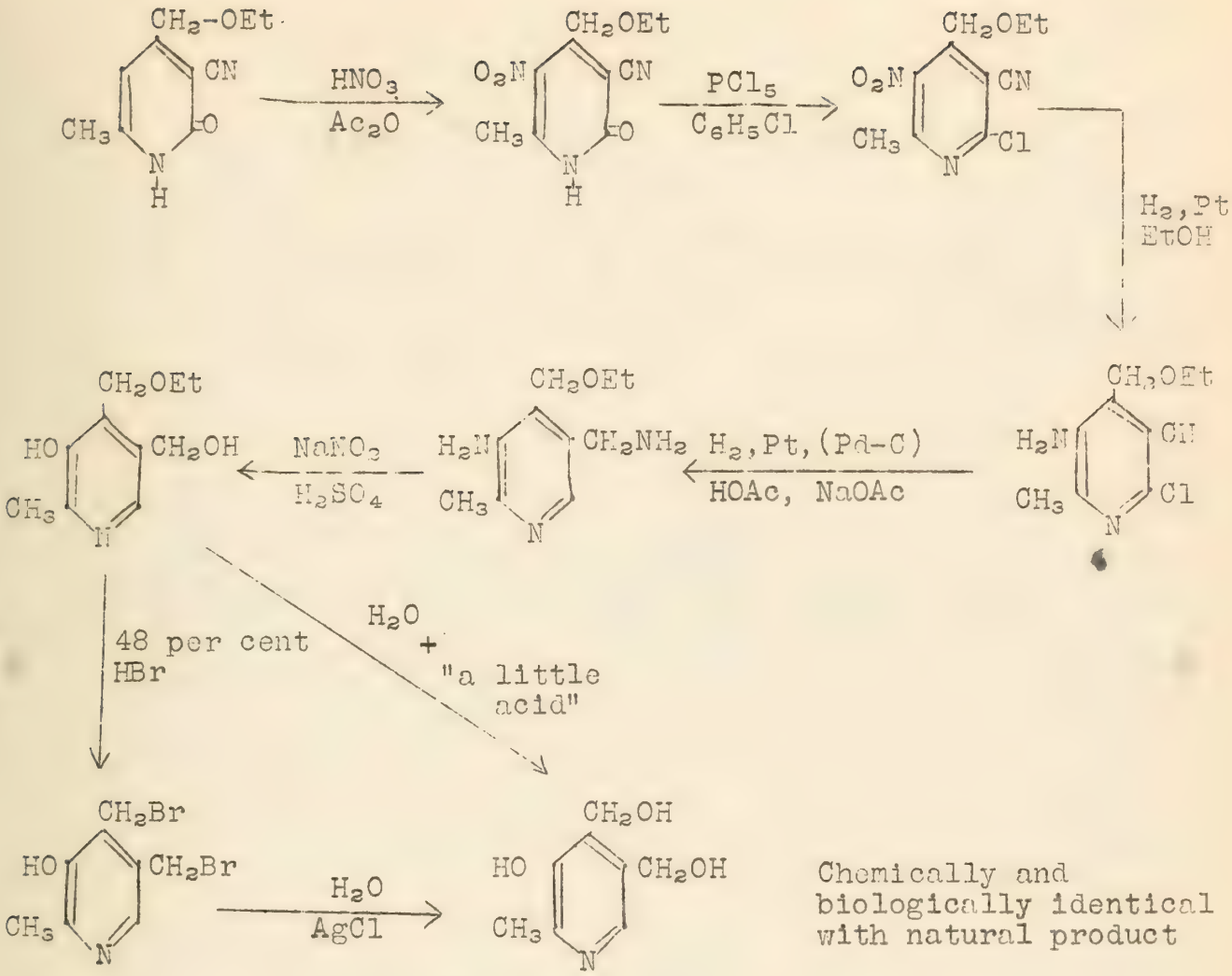
Synthesis of the dibasic acid (VIIa), by a method not described, and demonstration of its identity with the degradation product (VII) showed I to be the correct structure for adermin.

The degradation methods of Keresztesy do not differ in any important respects from those of Kuhn. The β-hydroxypyridine nucleus was indicated by ionization constant and absorption spectra studies. Similar oxidations of the methyl ether (II) were carried out to obtain the lactone (III) and dibasic acid (VII). The information thus obtained gave the same choice between two formulas as was faced by Kuhn. In this case I was picked over Ia, and consequently VIIa over VIIb, on the basis of the color reaction of adermin in alkaline solution with 2,6-dichloroquinone-4-chloroimide. A blue color fading to a reddish brown was produced. Phenols substituted in the <u>para</u>-position do not give this color.

On the basis of this information VIIa was synthesized and found to be identical with the degradation product (VII) from adermin methyl ether (II). The scheme of synthesis was as follows:

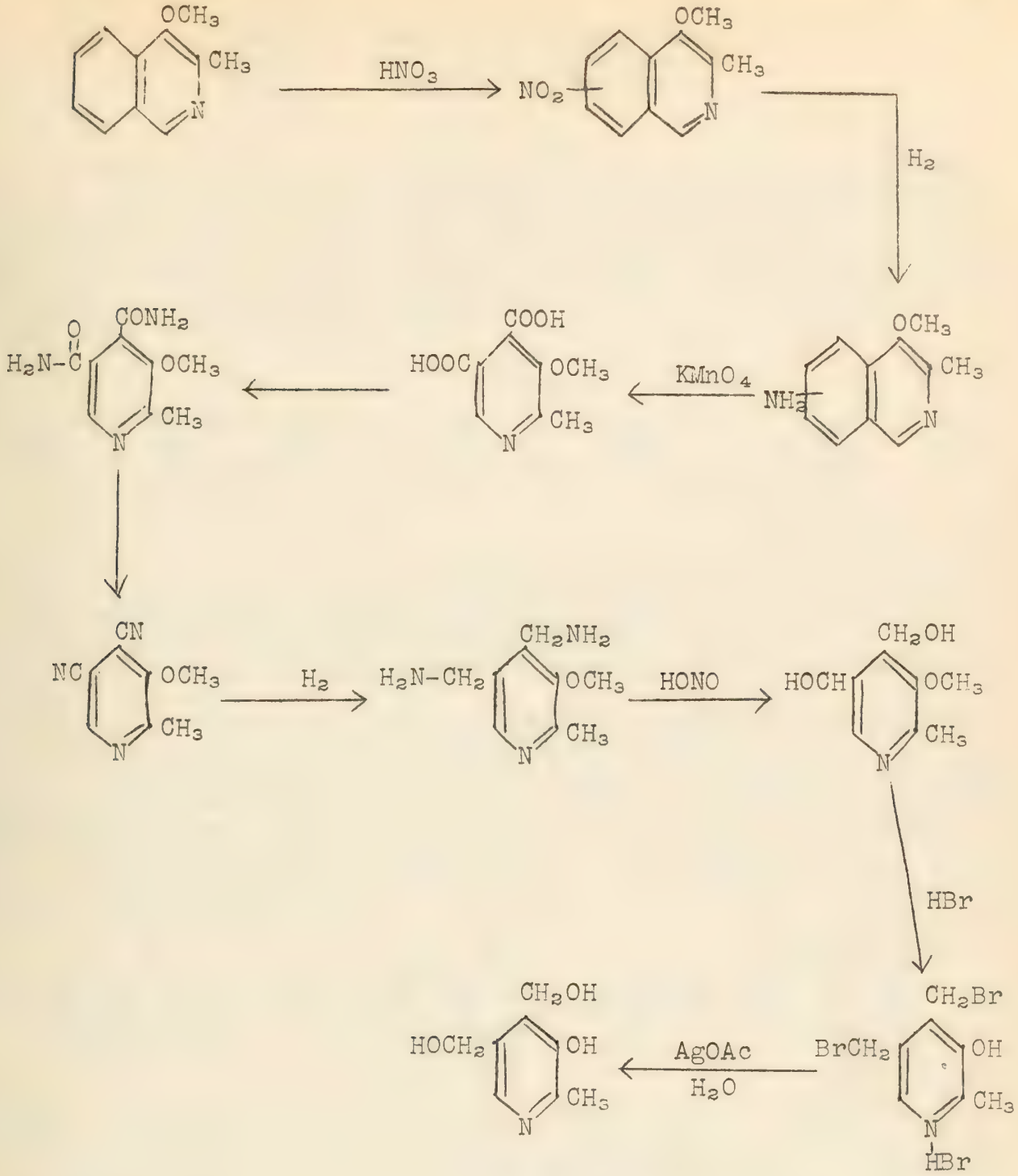


A somewhat similar scheme was used in the synthesis of adermin:



Chemically and biologically identical with natural product

Kuhn has announced, in a recent note, the synthesis of adermin by an entirely different method:



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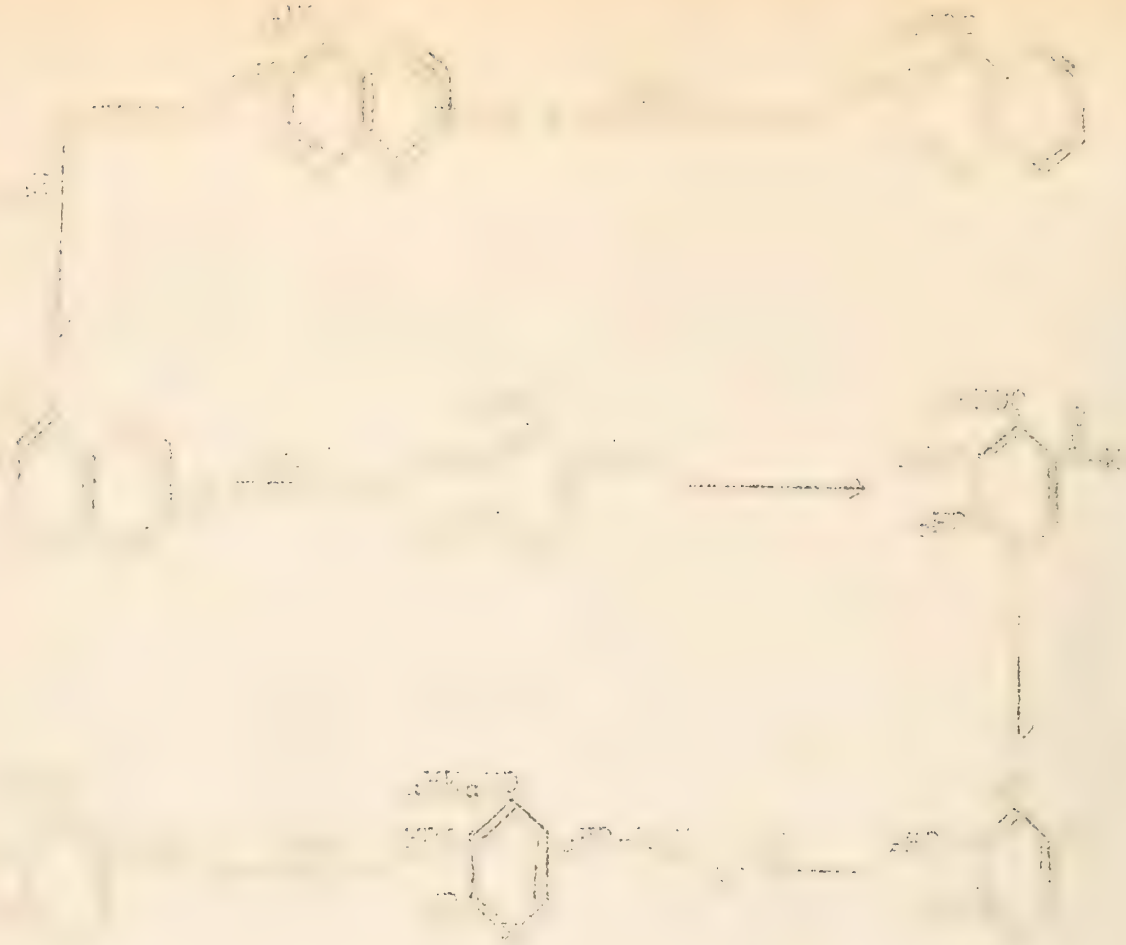
Kuhn et al., Ber., 71, 780, 1534 (1938); ibid., 72, 305 (1939); Naturwiss., 27, 469 (1939)

Keresztesy, Folkers, et al., J. Am. Chem. Soc., 60, 1267 (1938); ibid., 61, 1237, 1242, 1245 (1939).

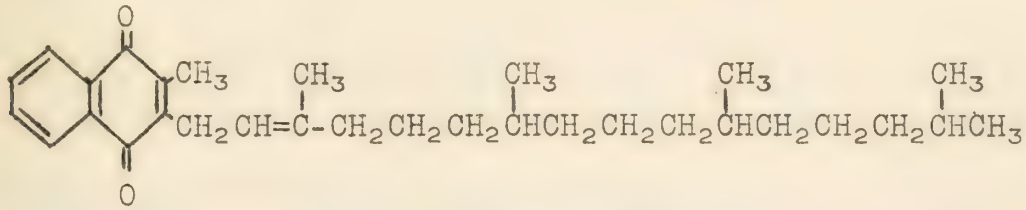
Reported by J. H. Clark
September 27, 1939.



THE STRUCTURE OF VITAMIN K_1

Dam -- University of Copenhagen
Doisy -- St. Louis University
Fieser -- Harvard University

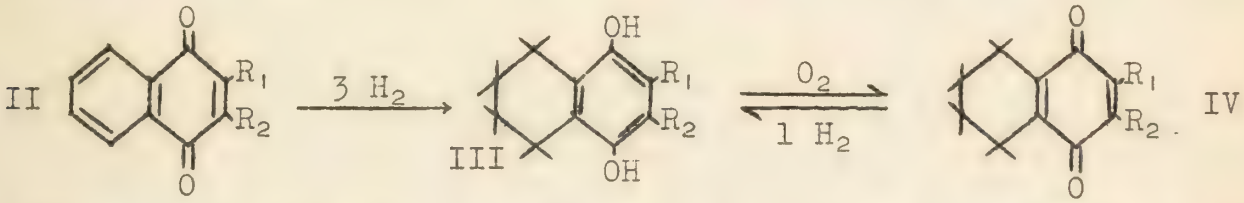
1934 Dam reported an antihemorrhagic factor which he called vitamin K. A deficiency of vitamin K in certain fowl produced internal hemorrhages and marked retardation of the clotting time of the blood. In April, 1939, Doisy reported the isolation of vitamin K_1 from alfalfa and the less potent K_2 from putrefied fish meal. By August 25, 1939, the structure of K_1 was shown independently by Fieser and Doisy to be 2-methyl-3-phytyl-1,4-naphthoquinone (I):



I

Analyses and molecular weight determinations on K_1 were not conclusive, but indicated the formula $C_{32}H_{48}O_2$. A 2-alkyl-3-phytyl-1,4-naphthoquinone was suspected from the following evidence:

1. Lability to light, heat and alkali, and the yellow color indicated a quinone.
2. Absorption spectrum of K_1 and K_2 resembled 1,4-naphthoquinones more closely than quinones of other series.
3. Reductive acetylation of K_1 gave the colorless diacetyl-dihydro K_1 which absorbed 3 moles of H_2. This diacetate was not readily hydrolyzed by acids or bases, indicating the presence of hindering substituents in the 2 and 3 positions.
4. The hydrogenation data for K_1 was interpreted alike by Doisy and Fieser as follows:



This would place one double bond in R_1 or R_2, since K_1 absorbed a total of 4 moles of H_2.

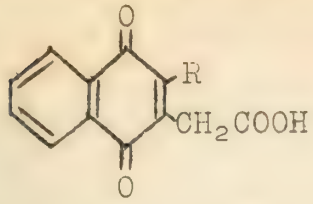
5. Ozonolysis by Doisy of the diacetate of the K_1 hydroquinone gave a ketone identified as 2,6,10-trimethylpentadecanone (VI) by comparison with an authentic specimen prepared by oxidation of phytol (V):

This pointed to a phytyl side chain in the vitamin molecule.

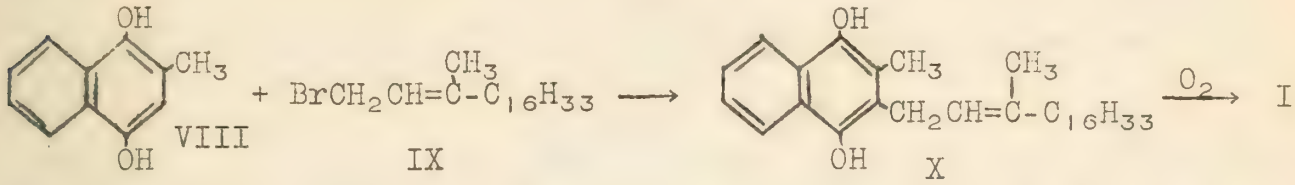
At this point Doisy continued with the degradative method, while Fieser attacked the problem from the synthetic angle.

Doisy: Chromic acid oxidation of K_1 gave 2 crystalline acidic compounds. One was identified as phthalic anhydride, which showed the benzenoid ring to be unsubstituted. The second acid (m. 210°) was a substituted naphthoquinone acetic acid (VII). Since the nucleus plus phytyl side chain accounted for all but 2 carbons in the formula $C_{32}H$

Doisy considered vitamin K_1 to be 2-ethyl-3-phytyl-1,4-naphthoquinone and thus the second acid (m. 210°) would be VII, R=C_2H_5. However, this 2-ethyl acid was synthesized and found to be different. Thereupon the 2-methyl acid (VII, R=CH_3) was synthesized and found to be identical with the oxidation product from K_1. This indicated structure I for vitamin K_1, which was confirmed by synthesis using Claisen's direct alkylation method with phytyl bromide (IX) and 2-methyl-1,4-naphthohydroquinone (VIII), followed by air oxidation:

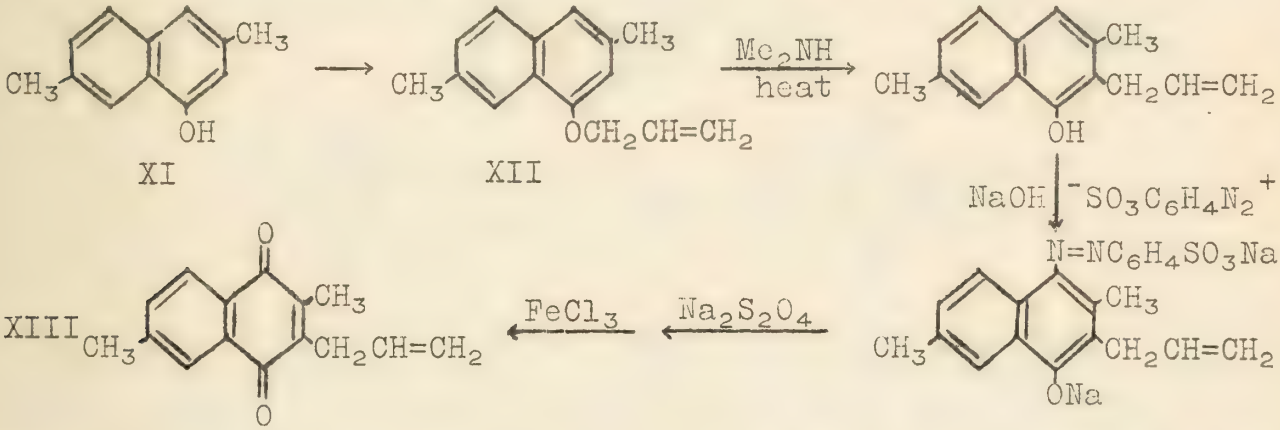


VII



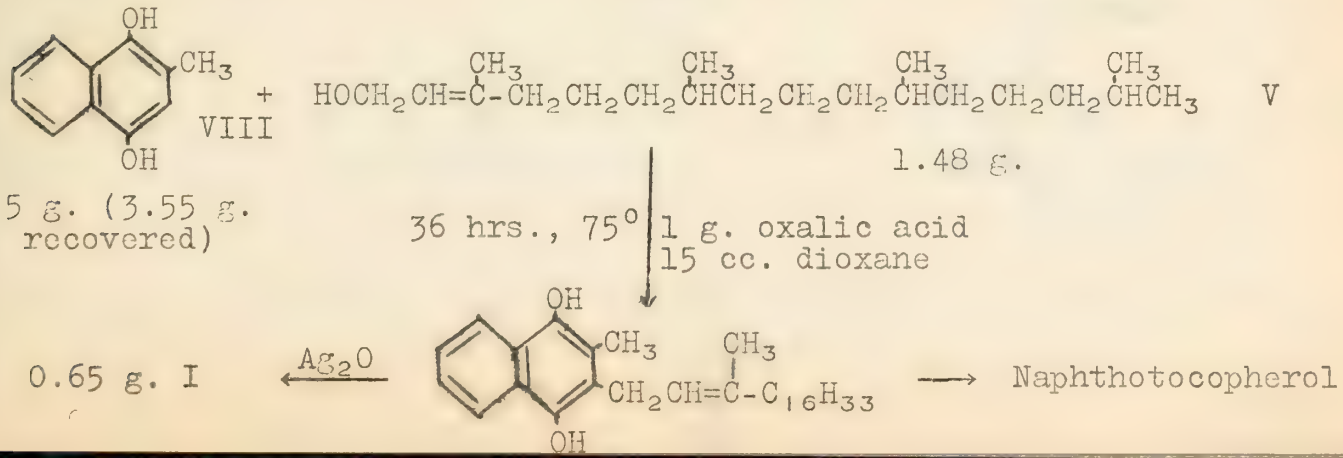
This synthetic compound was shown to be identical with natural vitamin K_1 by comparison of the analyses, melting points, and oxidation products of the diacetates from synthetic and natural vitamin K_1.

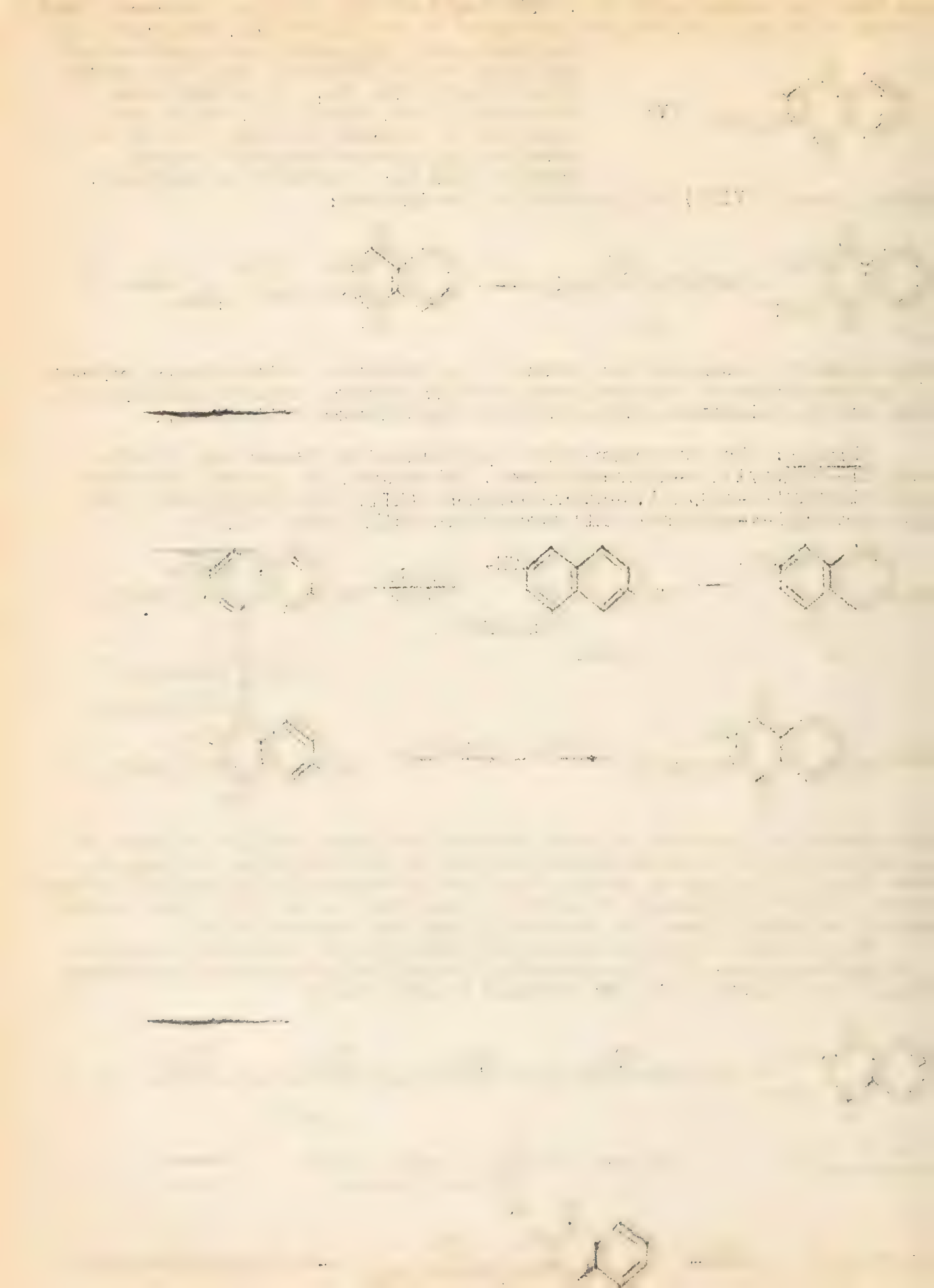
Fieser: The structure first postulated by Fieser was 2,6-dimethyl-3-phytyl-1,4-naphthoquinone. Thereupon, as a model substance 2,6-dimethyl-3-allyl-1,4-naphthoquinone (XIII) was synthesized from 2,6-dimethyl-4-naphthol (XI) through the allyl ether (XII):



The absorption spectrum of this compound was very similar to that of K_1 but shifted to a considerable extent in the direction of longer wave length, leading to doubt about the presence of the 6-methyl group; later, Doisy's isolation of phthalic anhydride as an oxidation product proved definitely that the benzenoid ring was unsubstituted.

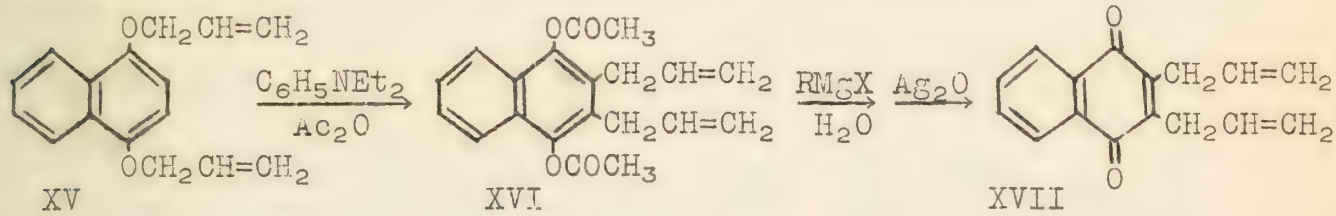
Fieser then concentrated on the synthesis of 2-methyl-3-phytyl-1,4-naphthoquinone (I) by condensing 2-methyl-1,4-naphthohydroquinone (VIII) with phytol (V) (cf. vitamin E synthesis):

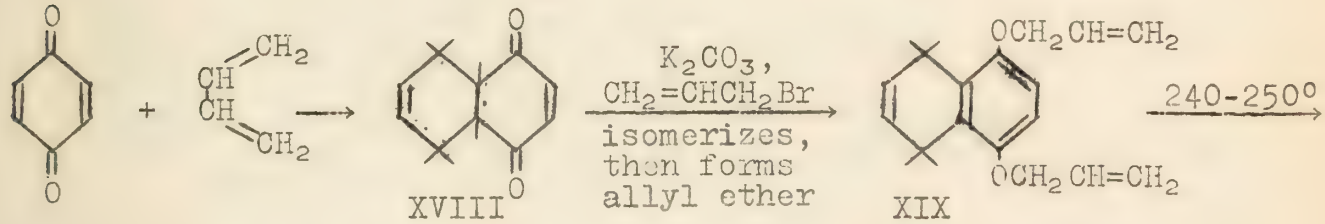


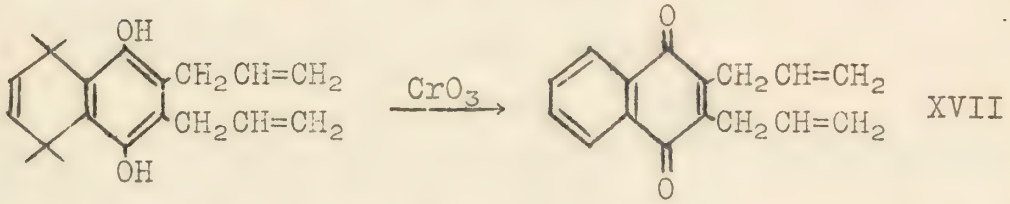


In all its properties (abs. spectrum, bioactivity, derivatives) this synthetic compound agreed with those of the natural vitamin K_1.

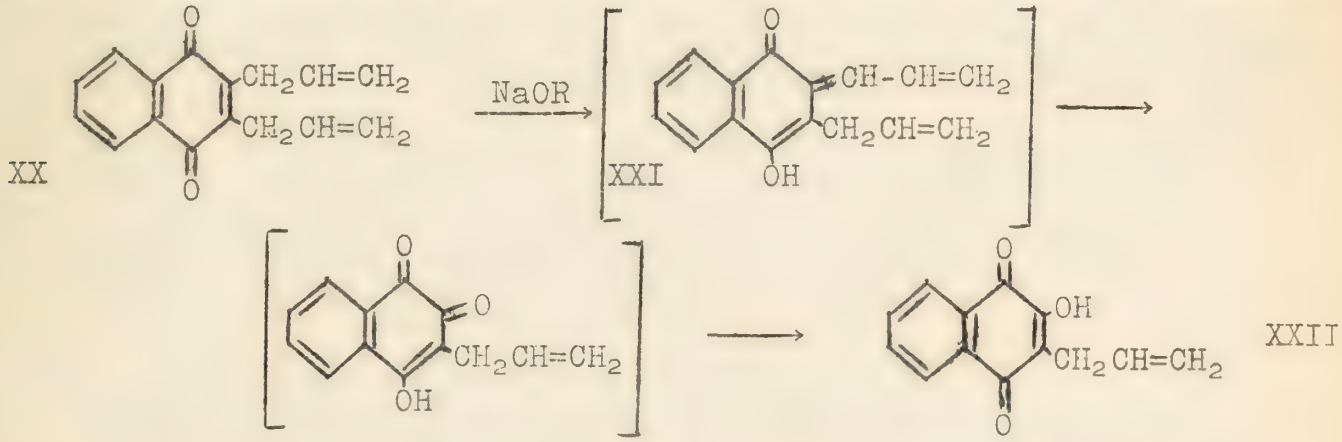
Color Reaction: Dam, Karrer, et al., reported the isolation of highly purified K_1 which gave with $NaOC_2H_5$ a transient purple color changing to reddish brown. Fieser noticed that all of his synthetic 1,4-naphthoquinones containing at least one allyl group (i.e. a β-unsaturated side chain) gave the same color change with alcoholic alkali. In the course of his synthetic work, Fieser synthesized 2,3-diallyl-1,4-naphthoquinone (XVII) as a model for the suggested structure for vitamin K_2 (2,3-difarnesyl-1,4-naphthoquinone). Two methods were used for this synthesis:





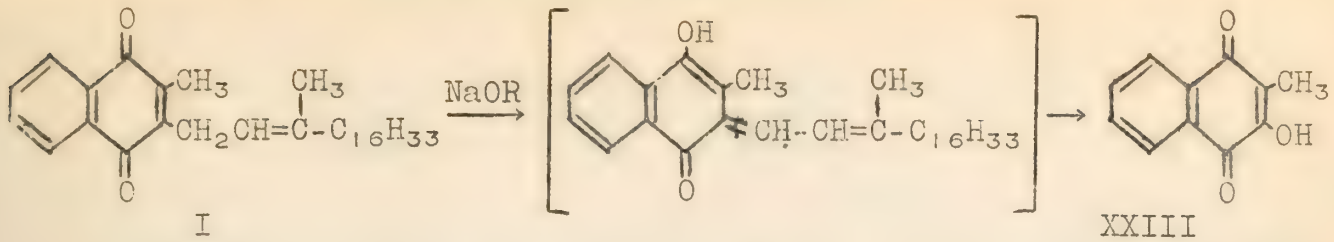


When XVII was treated with 10% aqueous KOH, the solution changed from indigo blue, through purple, to dull red. Extraction and acidification gave a yellow crystalline compound identified as 2-hydroxy-3-allyl-1,4-naphthoquinone (XXII). In analogy to the tautomerism of alkylated naphthoquinones recently studied by Fieser, he interpreted this color reaction as involving a tautomeric shift to XXI, followed by cleavage:



Thus it should be possible to degrade vitamin K_1 to phthiocol (XXIII)

Later, Fieser confirmed this with a sample of synthetic vitamin K_1:



It seems particularly interesting that 2-methyl-1,4-naphthoquinone is as highly active as vitamin K_1. Doisy has suggested its use as a basic assay standard.

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Reported by E. H. Riddle
September 27, 1939

THE CHEMISTRY OF SOME NATURALLY-OCCURRING β-HYDROXY-α-NAPHTHAQUINONES

Kuhn -- Kaiser-Wilhelm Institute
Fieser -- Harvard University
Hooker -- Private laboratory

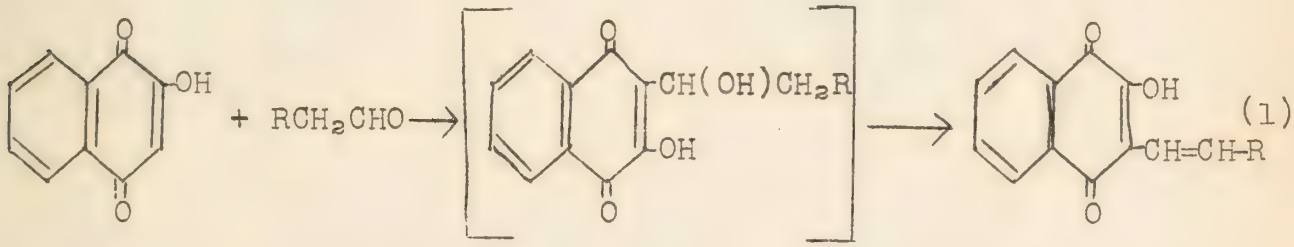
With the exception of echinochrome A, all the hydroxy naphthaquinones found in nature (juglon, lawsone, plumbagin, shikonin, alcannin, droserone, lapachol, and lomatiol) have been isolated from plant sources; echinochrome A has recently been extracted from the ovaries of a species of sea urchin. The present interest in vitamin K as well as this latter fact makes appropriate a survey of the chemistry of these compounds. We propose to treat some of the more significant reactions of β-hydroxy-α-naphthaquinones.

I. Some Reactions of Lawsone.

Fieser has prepared the oxygen ethers of the α- and β-forms of 2-hydroxy-α-naphthaquinone (lawsone) by treating its silver salt with an alkyl halide. Use of 3-chlorolawsone instead of lawsone gave only the α-ether and this in about 90 per cent yield. With diazomethane or acidified methyl alcohol only the α-ether was isolated. These facts led Fieser to the conclusion that the α- and β-forms of lawsone are tautomers and the ortho-quinone is present in extremely small concentrations.

Carbon alkylation is also possible; the yield depends directly upon the reactivity of the halogen and is especially good with allyl bromide, benzyl bromide, and triphenylmethyl bromide.

Aldehydes react with lawsone to give 1-hydroxy-2-alkenyl-α-naphthaquinones (eq. 1). This aldehyde synthesis was successful



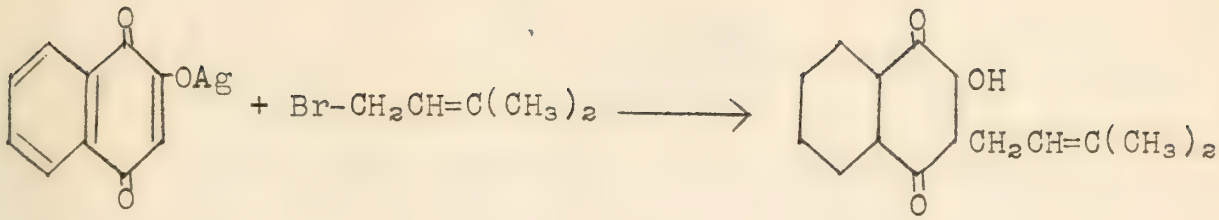
(1)

in the preparation of the propenyl, pentenyl, heptenyl, phenylvinyl and γ-phenylpropenyl derivatives.

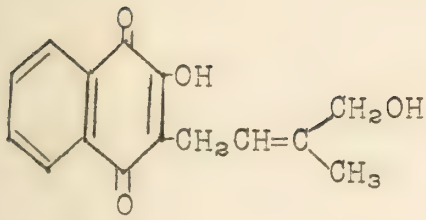
Irradiation of a warm aqueous solution of lawsone gives a 40 per cent yield of 3-bi-2,2'-α-naphthaquinone which, by several direct procedures, may be converted into the α,α'- (70 per cent), the α,β- (85 per cent), or the β,β'- (86 per cent) anhydrides.

II. The Chemistry of Lapachol (I) and Lomatiol (II).

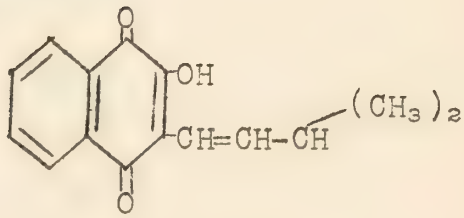
Following the method of carbon alkylation noted above, Fieser has synthesized lapachol by the reaction



I. Lapachol



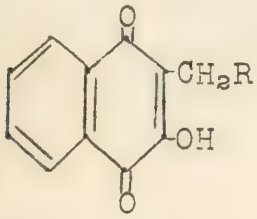
II. Lomatiol



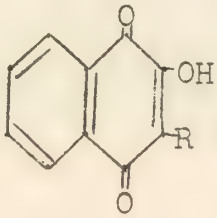
III. Isolapachol

By the aldehydo synthesis Hooker has obtained isolapachol from lawsone and isovaleraldehyde.

In the oxidation of lapachols (IV) with alkaline permanganate the sidechain carbon atom nearest the quinone ring is removed as carbon dioxide and a new lapachol (V) is formed. The course of the reaction is apparently the same if the R group contains a



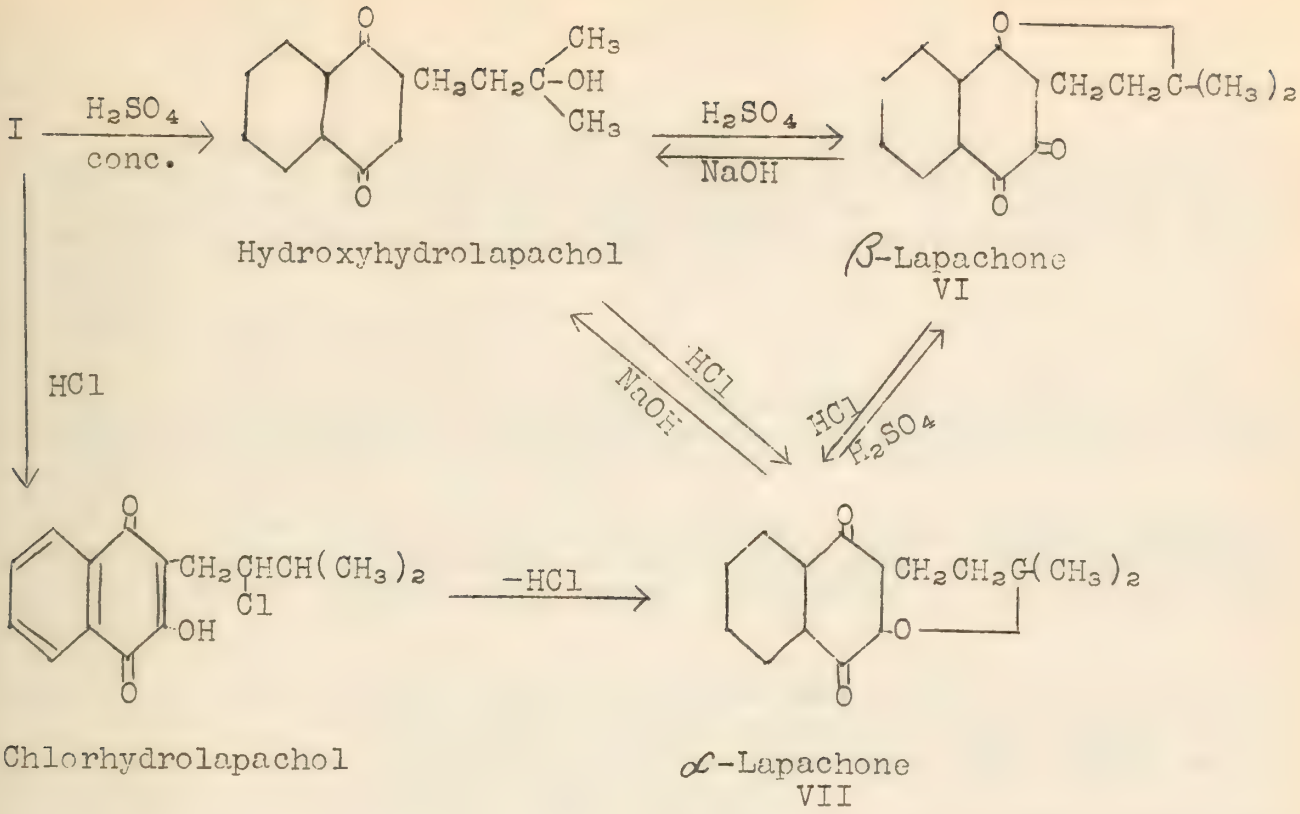
IV



V

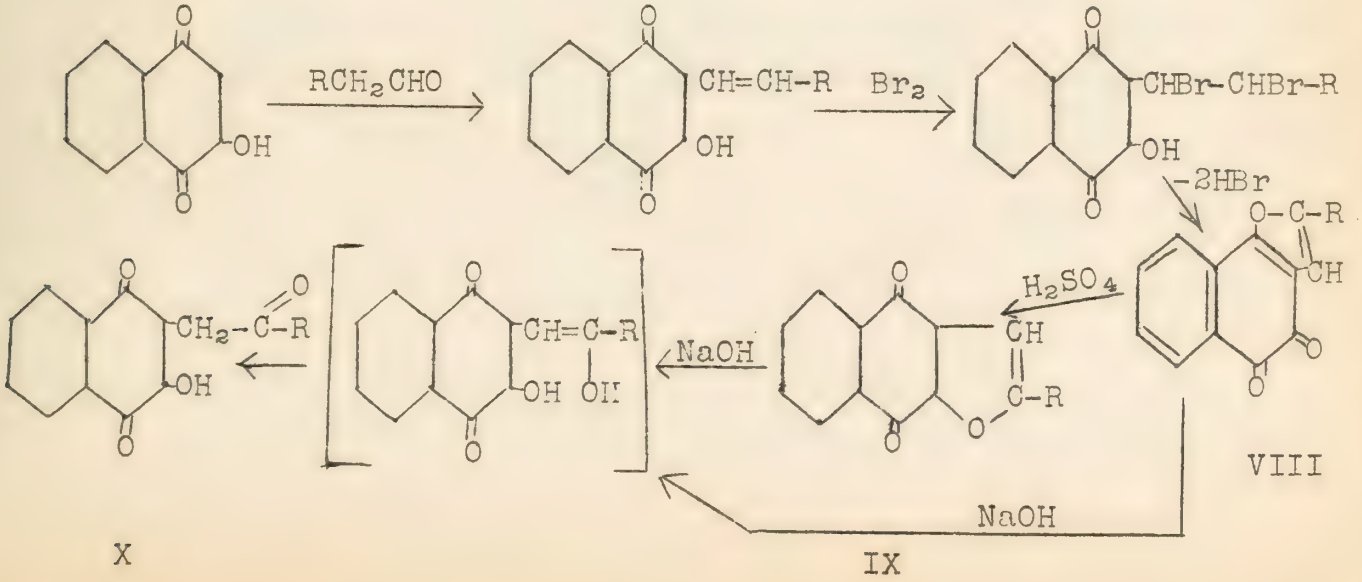
double bond, as in lapachol, or a hydroxyl group, as in lomatiol.

Characteristic reactions of lapachol with acids and bases are sketched below.



The above interconversions have been accomplished also with α,β,β'-dimethylvinyl-3-hydroxy-α-naphthaquinone; the lapachones here have, of course, five-membered rings.

The synthesis of furan derivatives of α- and β-naphthoquinones and their hydrolysis to ketonic compounds is indicated below. Note that in this series, the concentrated sulfuric acid gives the <u>para</u>-quinone rather than the <u>ortho</u>-quinone. The reduction of the ketones (X) to secondary alcohols by hydrogenation (platinum) is thought by Fieser to be general for these compounds.



The lapachols are yellow unless a double bond is present in the α-position on the alkenyl sidechain whereupon the compound is red to orange. With ortho-phenylenediamine, the lapachols give eurhodols, β-lapachones give true azines, and α-lapachones do not react.

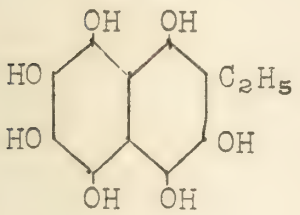
III. Echinochrome A.

This dyestuff possesses the unique biological property of activating the sperm of sea urchins to copulation. This biological activity appears at dilutions of 10^{-9}.

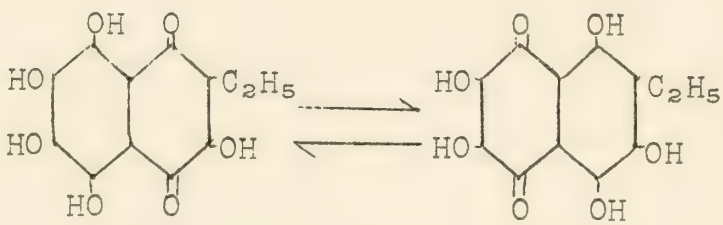
Extraction of ovaries of the sea urchin Arbacia pustulosa with an acetone-acetic acid-water mixture gave as much as 11 mg. of this active material per ovary. The steps in its identification were:

1. The empirical formula was found to be $C_{12}H_{10}O_7$.
2. Reductive acetylation gave a heptaacetate.
3. Diazomethane gave a trimethyl ether which was further characterized.
4. Distillation with zinc dust gave small amounts of naphthalene.
5. Chromic acid oxidation gave 0.83 moles of propionic acid which was further characterized.

This information leads to the formula XI for the leuco compound since the reactions, absorption spectra, and redox-potential of the echinochrome A indicate it to be a quinone. Color reactions support the equilibria formulas XII and XIII for the dyestuff.



XI



XII XIII

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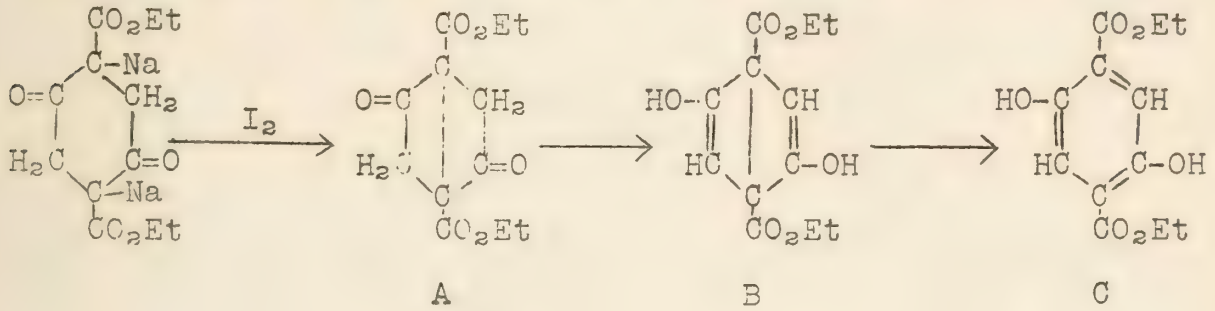
Reported by R. O. Sauer
October 4, 1939.

PARA-BRIDGE STRUCTURES BY USE OF SUCCINO-SUCCINIC ESTER

Guha -- Indian Institute of Science, Bangalore, India

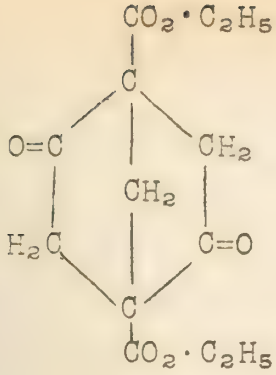
Baeyer tried the experiments, evidently without success, of bridging the p-carbon atoms of succino-succinic ester with methylene iodide or ethylene bromide. Meerwein, who attempted to form a spiroindless tricyclic system from bicyclononanedione tetracarboxylic ester, attributed the failure to the splitting up of the bridge compounds by alkali. Recently, however, Komppa obtained bicyclo (2,2,2,-octanone out of hexahydrohomoterephthalic acid; and also by means of the Diel's syntheses it is possible to make bicyclo (1,2,2)-heptane and bicyclo-(2,2,2)-octane derivatives out of substituted cyclopentane or conjugated cyclohexane derivatives. However, the Diel's method has its limitations.

The disodium compound of succino-succinic ester gives with methylene iodide dihydroxyterephthalic ester (C). This can be explained through the assumption that methylene iodide sets free iodide, that gives the unstable bicyclo-(0,2,2)-hexane derivative (A), which enolizes to B (corresponding to the Dewar's benzene model), and it quickly changes into the stable Kekule form (C). This assumption has proven itself correct through the discovery that succino-succinic ester when treated with bromine or iodine gives the same 2,5-dihydroxyterephthalic ester.



A B C

After a large number of attempts made under varying experimental conditions, the desired bridge formation has now been effected. By heating the dry sodium compound of succino-succinic ester with methylene, ethylene and trimethylene bromides are bicyclo-(1,2,2)-heptanedione dicarboxylic ester (I), bicyclo-(2,2,2)-octanedione dicarboxylic ester (II), and bicyclo-(3,2,2)-nonanedione dicarboxylic ester (XIX), respectively, obtained. II and XIX are easily hydrolyzed by heating with hydrochloric acid to the corresponding acids (III and XX). It is remarkable to note that these bridged esters cannot be decarboxylated under conditions in which succino-succinic ester readily gives 1,4-dihydroxycyclohexadiene. That the reactions have not taken place in the enolic phase, is proven by the fact that the bridged compounds give sharp melting disemicarbazones.



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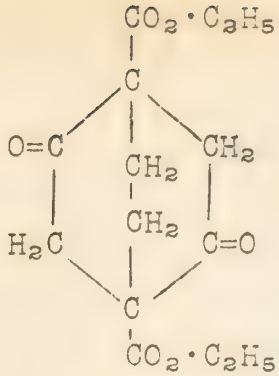

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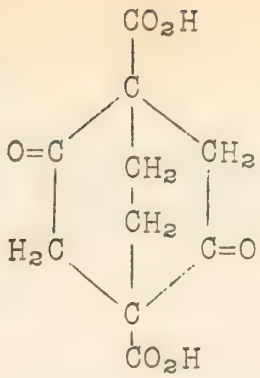

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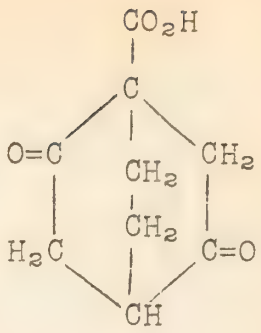

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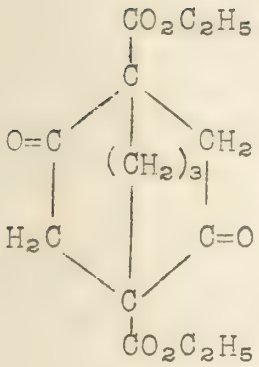

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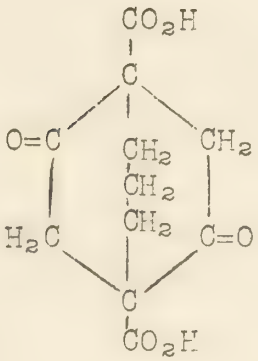

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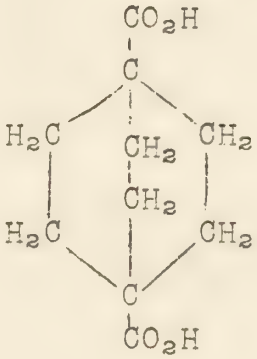

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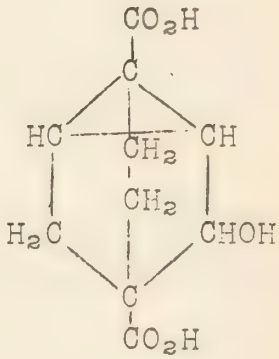

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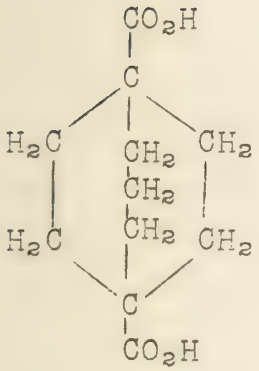

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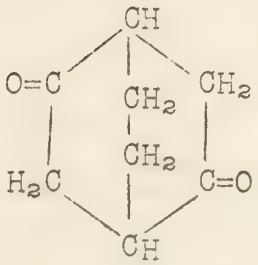

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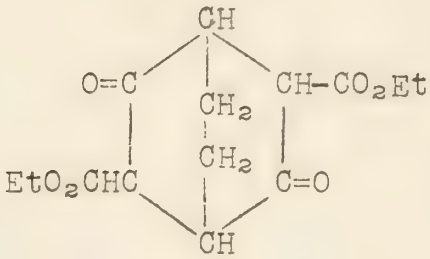

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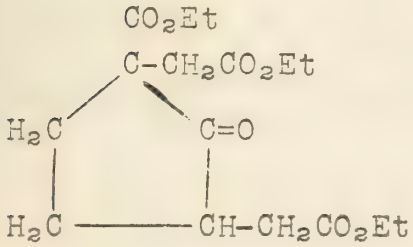
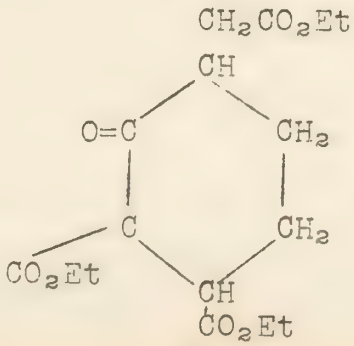


VIIIa



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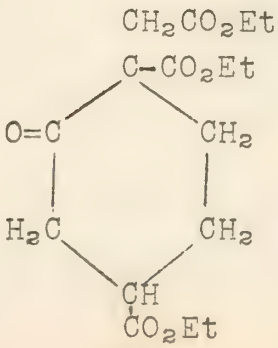

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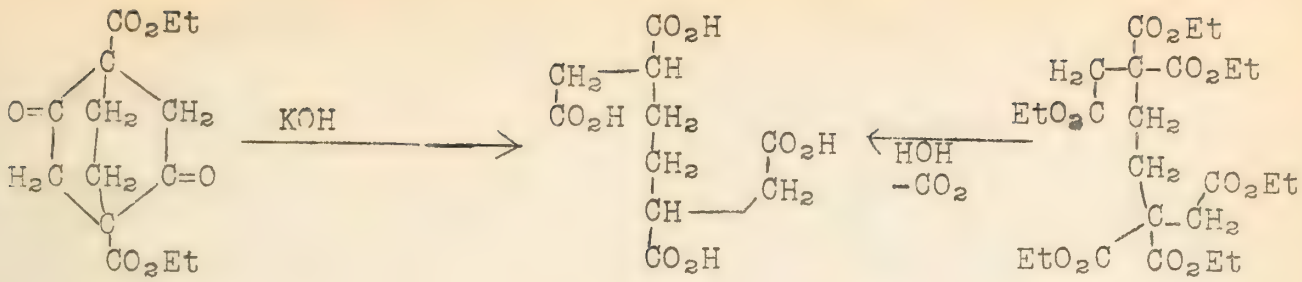


II X XI

The compound II undergoes by treatment with alcoholic potash ring cleavage to yield what appears to be β,β'-dicarboxysuberic acid as yet unreported in the literature. This latter compound was then synthesized (1) by the action of ethylene bromide on carbethoxy succinate and (2) by the action of ethyl bromacetate upon ethyl butane and tetracarboxylate. The acids obtained by these two methods were identical to that obtained by cleavage of compound II.

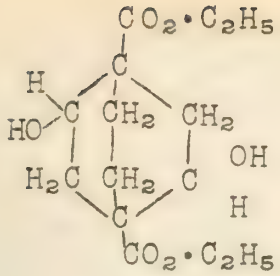
Compound II gives, by the treatment with 1.5 per cent neutral permanganate solution, an acid mixture out of which oxalic acid was definitely isolated. Use of fuming nitric acid gave the same oxidation products.

The next step was to attempt to convert the bicyclic compound II to the parent hydrocarbon bicyclo-(2,2,2)-octane. Two ways seemed possible, (1) the $-CO_2-C_2H_5$ groups are displaced by hydrogen and then the keto groups of the decarboxylated products are reduced to the $-CH_2-$ groups, and (2) the reduction of the keto group to $-CH_2-$ group and then the decarboxylation of the reduced acid. By use of the first method, it is indeed easy to hydrolyze the ester groups, but it was not possible to split out two moles of carbon dioxide either by prolonged heating with hydrochloric acid, sulfuric acid, or by heating the acid in an autoclave under high pressure and temperature. Only one mole of carbon dioxide can be obtained by heating the free dibasic acid (III), giving the acid (IV). The use of alkali reagents is not suited because the ring would be cleaved. The reduction of the keto group in the second method was attempted in various ways. The action of sodium amalgam and catalytic hydrogenation by use of platinum oxide as catalyst gave two different dihydroxy compounds.

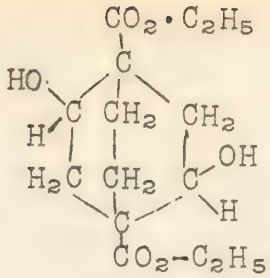
	B.P.	d_4^{20}	n_D^{30}
Product from Na (amalgam)	200-204°	1.1725	1.4760
Product from catalytic reduction	195-196	1.1810	1.4800

Their analyses and $(R_L)_D$ checked with the calculated values.

The product obtained from reduction with sodium amalgam was given the <u>trans</u>-form formula (XII) and the product obtained by catalytic reduction was given the <u>cis</u>-form (XIII):



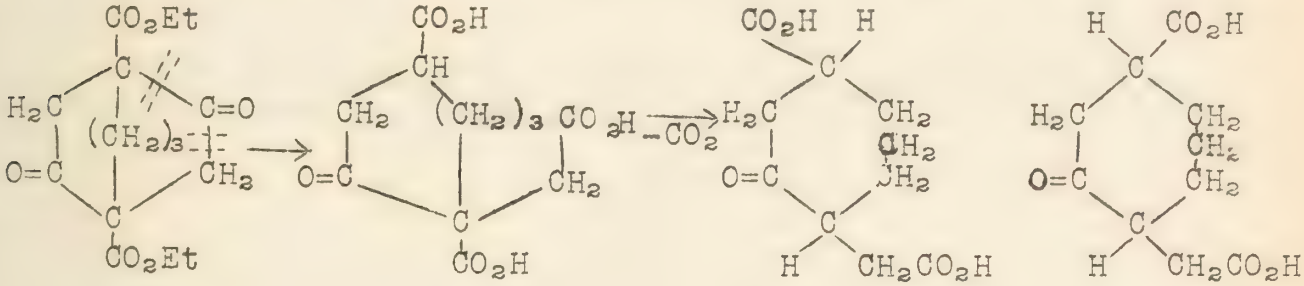
XII



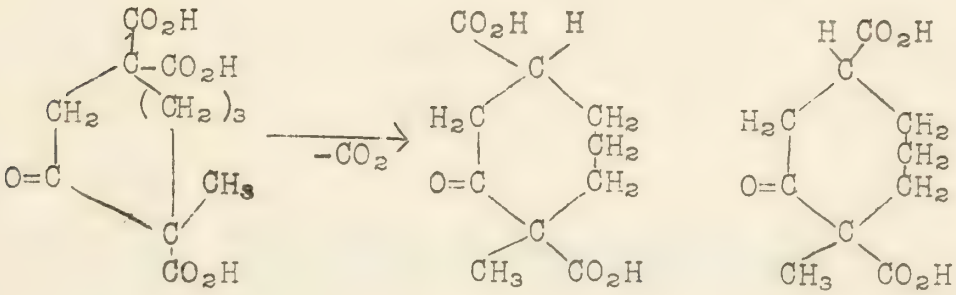
XIII

The reduction of bridge ester (II) by Clemmensen's method gave bicyclo-(2,2,2)-octane dicarboxylic acid (XIV), together with a monohydroxy acid (XVI).

The bicyclic compound (XIX) reacts with alcoholic potash to give a mixture out of which three acids were isolated. Two of them were identified as being either XXIV and XXV or XXVI and XXVII.

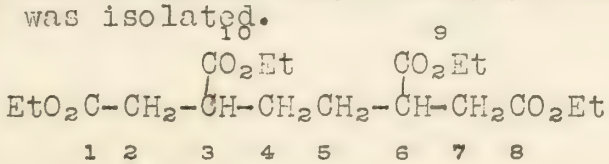


XXIV XXV



XXVI XXVII

The reduction of compound XIX by way of Clemmensen gave a mixture out of which bicyclo-(3,2,2)-nonane dicarboxylic acid (XXVIII) was isolated.



V

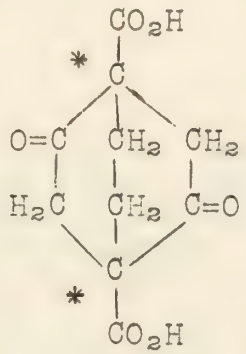
The cyclization of β,β'-dicarbethoxysuberic ester (V) was attempted by the Dieckman's condensation, and it was possible to isolate bicyclo-(2,2,2)-octanedione (VI).

By looking at formula V, you can recognize that theoretically it can be cyclized in various ways, (a) through cleavage of 2 moles of ethyl alcohol, bicyclo-(2,2,2)-octane derivative II and VII are obtained, (b) through the cleavage of 1 mole of alcohol compounds VIIIa, VIIIb, VIIIc, are obtained.

These compounds could be characterized and identified by their solubility in alkali and their behaviour with boiling hydrochloric acid. Compound VI was thus isolated by these methods. Hence, by means of the double Dieckman's condensation a new and easy way of preparing the bicyclic diketone (VI) is given.

As one will observe, formula III contains two asymmetric carbon atoms, so it should be possible to isolate the optical isomers. Two active isomers were obtained using brucine, and the physical properties of the isomers differed from that of the inactive form.

This isolation of the active isomers is another proof for the correctness of formula III.



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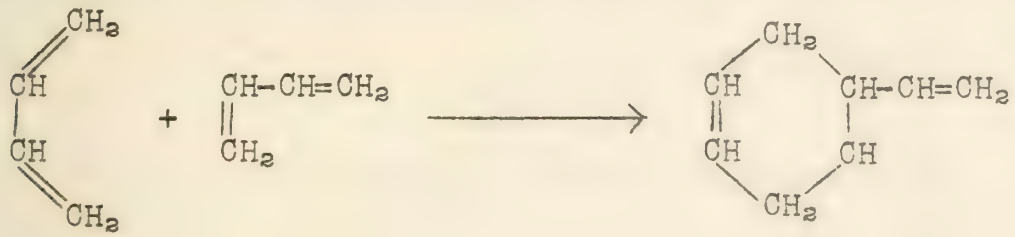
Reported by J. F. Kaplan
October 4, 1939.

THE POLYMERIZATION OF BUTADIENE

Hill, Lewis and Simonsen -- University of North Wales

Butadiene and certain of its derivatives and homologs may be polymerized by a variety of methods and catalysts. These compounds are of considerable technical importance because of their similarity to natural rubber. The properties of these polymers are determined by the particular diene which constitutes the monomeric unit and also by the mode of polymerization. In the United States the chief source of synthetic rubber is chloroprene while in Germany butadiene is the sole diolefin constituent of the so-called Bura rubbers.

Polymerization of butadiene may proceed in a number of ways. At higher temperatures (80-90° C.) and in the absence of an active polymerizing agent an oily, liquid dimer (I) is formed.



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Higher polymers may be formed by use of suitable catalysts or polymerization methods. Addition may occur through the 1,4- or the 1,2-positions or may be a random mixture of 1,4- and 1,2-addition. In the production of synthetic rubber from butadiene the following two methods give the most satisfactory products.

1. Polymerization in either the liquid or gaseous phase using metallic sodium as the polymerizing agent at a temperature of 30-40° C.

2. Polymerization by the formation of an emulsion of butadiene with a suitable emulsifying agent usually sodium oleate. A polymerizing catalyst is not necessary but peroxides are sometimes used. A temperature of 50-70° C. is most suitable. The result is a milky emulsion similar to latex from which the polymer is coagulated by addition of acids, alkali salts or similar coagulating agents. Concentrations as high as 40 per cent butadiene may be used.

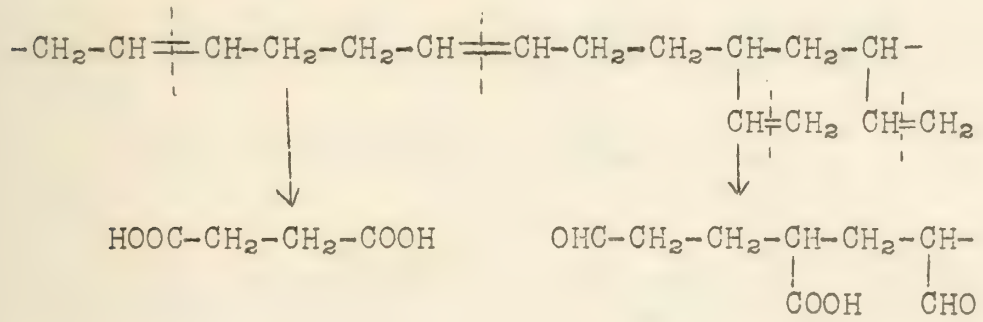
The emulsion method is generally used when it is desired to prepare from butadiene copolymers with unsaturated compounds of the acrylic type; being so modified because of the more desirable properties for certain uses.

The early work of Harries and the later work of Pummerer on the degradation of natural rubber by ozonolysis have shown that rubber consists of a symmetrical long chain polymer of isoprene

I

units combined by 1,4-addition. This conclusion was based on the formation of levulinic aldehyde on decomposition of the ozonide. Methyl glyoxal, acetaldehyde and formaldehyde were also obtained in small amounts but it seems possible that these were due to disproportionation at the ends of the chain.

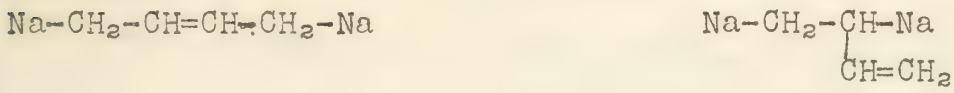
Pummerer has applied the same method to an investigation of the polymer formed from butadiene by sodium activated polymerization. The results have not been entirely successful since he has been unable to account for all of the carbon chain after degradation. The chief product of the decomposition was a white powder having the characteristics of a high polymer and which appeared to be an aldehyde-acid with the aldehyde group somewhat in excess (III). A small amount of succinic acid (II) was also isolated. The formation of these products indicates a mixed 1,4-1,2-addition with the 1,2-addition predominating.



II III

The supposed polymer and the ozonolysis products are shown above.

Ziegler, and also Abkin and Medvedev, have investigated the mechanism of the sodium activated polymerization and conclude that butadiene first undergoes a slow activation through the formation of a disodium compound (IV or V).



IV V

This compound is then capable of rapid reaction through a chain mechanism with butadiene molecules to form a higher polymer of the type

$$Na-(C_4H_6)_n-Na$$

VI

The reaction may be slowed by the use of sodium alkyls to form

$$R-(C_4H_8)_n-Na$$

VII

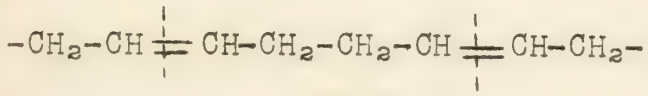
thereby creating a chain with only one active end. Chain length

of the resulting polymer, and consequently the viscosity, may be controlled by addition of various reagents which will react with the activated chain removing the sodium form from the molecule and irreversibly destroying its activity. Ziegler also states that on the basis of the results of this work the random 1,4-1,2-addition type of structure appears most plausible.

Hill, Lewis and Simonsen have extended the ozonolysis method of investigation to the butadiene polymers and copolymers prepared by the emulsion method. The coagulated polymers were treated with ozone and after decomposition the volatile aldehydes were removed by steam distillation. The nonvolatile residue was oxidized, the resulting acids isolated, esterified and separated by fractionation.

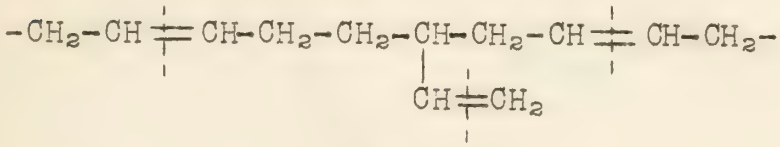
From the decomposition of the pure butadiene polymer the following products were isolated:

1. Succinic acid and succindialdehyde (as the dimethyl ester and the 2,4-dinitrophenylhydrazone). These result from 1,4-addition



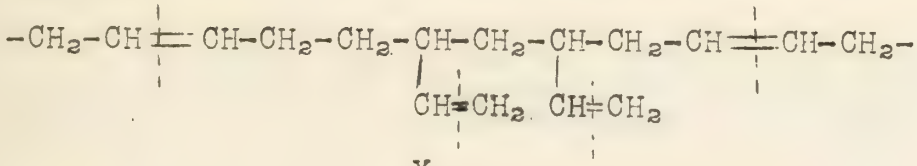
VIII

2. Butane-1,2,4-tricarboxylic acid (as the trimethyl ester). This is due to 1,4-1,2-1,4-addition, thus:



IX

3. A neutral higher ester resulting from sections of the chain where 1,2-addition has predominated or where chain branching has occurred.



X

4. A resinous acid which could not be completely esterified and evidently consisting of more complex units formed by predominant 1,2-addition and by chain branching.

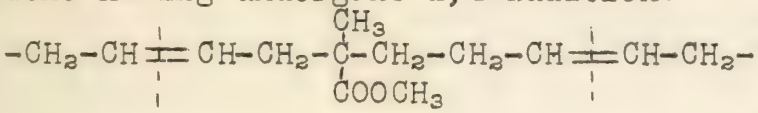
These results show that the emulsion polymer is formed by more or less random addition through both the 1,4- and 1,2-positions. Chain branching was indicated by the low solubility. No formaldehyde was isolated but small amounts of carbon dioxide and of formic acid were found. These may be formed in the decomposition of the vinyl sidechain

The copolymer of butadiene and methyl methacrylate was prepared by the emulsion method using equimolecular quantities of each.

Solubility of the polymer showed practically no cross linkage. After ozonolysis and decomposition the following products were isolated.

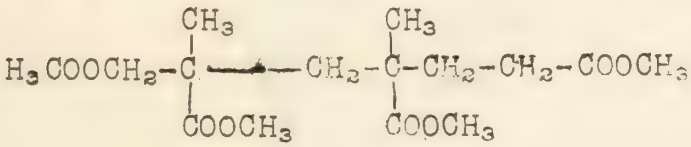
1. Succinic acid and succindialdehyde which indicates 1,4-addition of butadiene molecules as in VIII.

2. 2-Methyl butane-1,2,4-tricarboxylic acid (as the trimethyl ester). This is the major product and is due to alternate arrangement of butadiene and methyl methacrylate molecules, the butadiene having undergone 1,4-addition.

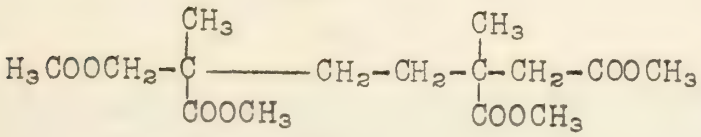


XI

3. A tetracarboxylic ester having the composition $C_{12}H_{14}O_4(OCH_3)_4$ which may be either



XII



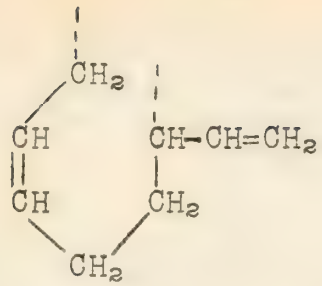
XIII

These acids are due to the adjacent linkage of two methyl methacrylate molecules, the particular acid formed being dependent on whether they are linked head-to-head and tail-to-tail or head-to-tail.

4. A neutral ester residue which is due to fragments of the molecule in which more than two methyl methacrylate molecules are linked together or where 1,2-addition of butadiene has occurred.

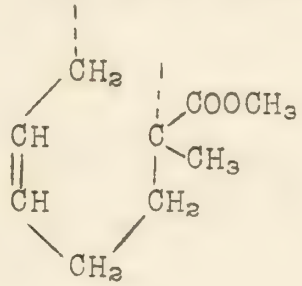
From these results it is shown that the copolymer consists of a chain more than half of which is made up of alternate methyl methacrylate and butadiene molecules, the butadiene having undergone 1,4-addition. The presence of adjacent methyl methacrylate units is demonstrated but adjacent butadiene units are scarce. The striking feature is that 1,4-addition of the butadiene molecules should be so predominant.

The same investigators, on the basis of this investigation, propose the following mechanism for the emulsion type of polymer. Two molecules of butadiene form an activated complex (XIV) in a manner similar to the dimerization reaction.



This would occur at the aqueous interface and would be capable of reacting with butadiene molecules by 1,4- or 1,2-addition, or with further similar complexes thus propagating a chain.

Similarly in the case of the copolymer a dimer complex (XV) would serve to activate the chain growth.



XV

From these considerations it might seem likely that the emulsion polymerized butadiene copolymer would most closely approximate natural rubber. It appears from X-ray studies that spatial and stereochemical factors may also be involved and that the rubber-like properties are at least somewhat dependent on these relationships.

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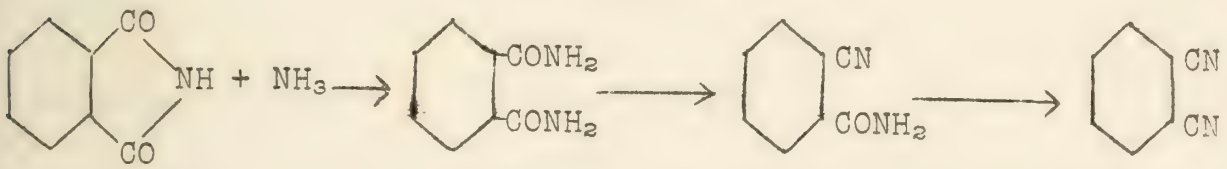
Reported by J. R. Cummings
October 11, 1939.

PHTHALOCYANINS AND RELATED COMPOUNDS

Linstead -- Imperial College, London
Helberger - Organisch-Chemisches Institute
der Technischen Hochschule,
München

The scientific investigation of phthalocyanins was started by a chance observation made in 1928 in a plant of Scottish Dyes, Ltd. Traces of a deep blue pigment were found in the phthalimide. Investigation showed this pigment to be a member of a new class of pigments now called "macrocyclic pigments."

Preparation.--Analysis showed 4 to 1 ratio of carbon to nitrogen, the presence of hydrogen and iron but no oxygen. Since the phthalimide was made by passing ammonia into phthalic anhydride Linstead tried to react phthalimide with more ammonia in an attempt to split out water.



I II

The products of this splitting out of water are o-cyanobenzamide (I) and phthalonitrile (II). Both these compounds are useful as intermediates in the preparation of phthalocyanin. On heating the above with various metallic reagents intensely colored compounds were obtained.

Reactions with Metals.--The first metals employed in the synthesis of these pigments were magnesium and iron but these were difficult to keep clean. Soon it was found that copper phthalocyanin was very readily prepared and easily purified. The free phthalocyanin could be prepared readily by treating the magnesium phthalocyanin with cold concentrated sulfuric acid. It was soon shown that the simple metallic combinations all had the general formula $(C_{32}H_{16}N_8)X$ (where X is a bivalent metal). Thus the phthalocyanins were prepared by the addition of four phthalonitrile molecules with the metal or by the reaction of four o-cyanobenzamide molecules and a metal with the loss of four moles of water.

The metal is very firmly attached in some phthalocyanins. Thus copper or iron phthalocyanins cannot be removed without destroying the molecule but magnesium or sodium are easily removed.

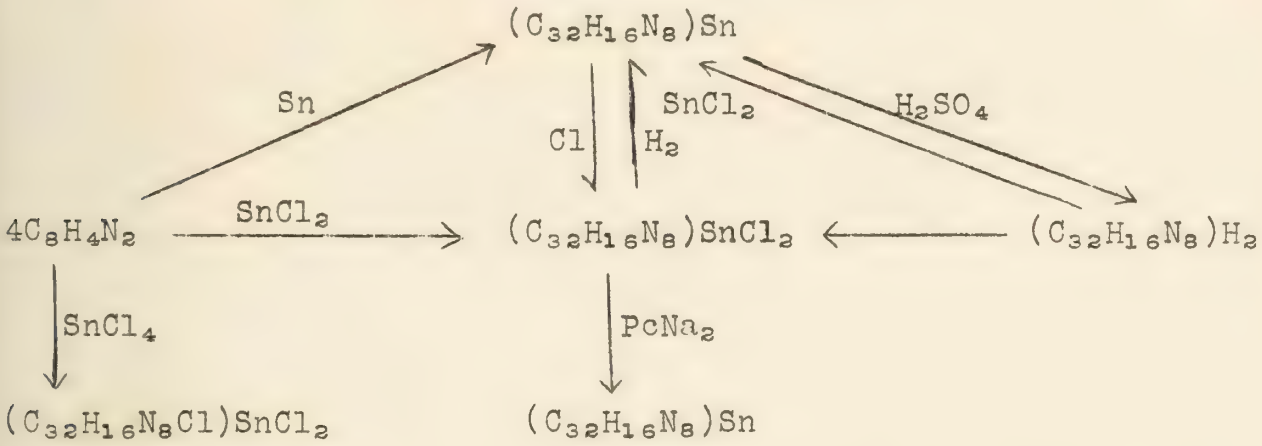
The metal phthalocyanins are prepared in a number of ways. Generally the reactions take place with the free metal but metal salts also can be used in the preparation of phthalocyanins. Thus:

$$Cu_2Cl_2 + 4C_8H_4N_2 \longrightarrow (C_8H_4N_2)_4Cu + CuCl_2$$

$$CuCl_2 + 4C_8H_4N_2 \longrightarrow (C_8H_4N_2)_3Cu(C_8H_3N_2Cl) + HCl$$

In this case one of the chlorine atoms go into the ring, in the four position. The Na_2 phthalocyanin is made from the $NaOC_2H_5$.

Tri- and tetravalent metals can also form phthalocyanin. Thus $AlCl_3$ reacts with four moles of phthalonitrile to produce $(C_8H_4N_2)_3AlCl(C_8H_3N_2Cl)$. Tin has a whole series of transformations which can be best shown in the following sketch.



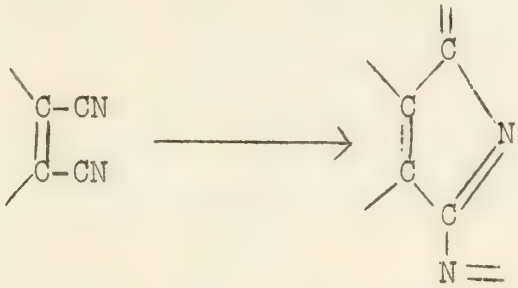
Linstead and his coworkers have prepared phthalocyanin derivatives of twenty-six elements.

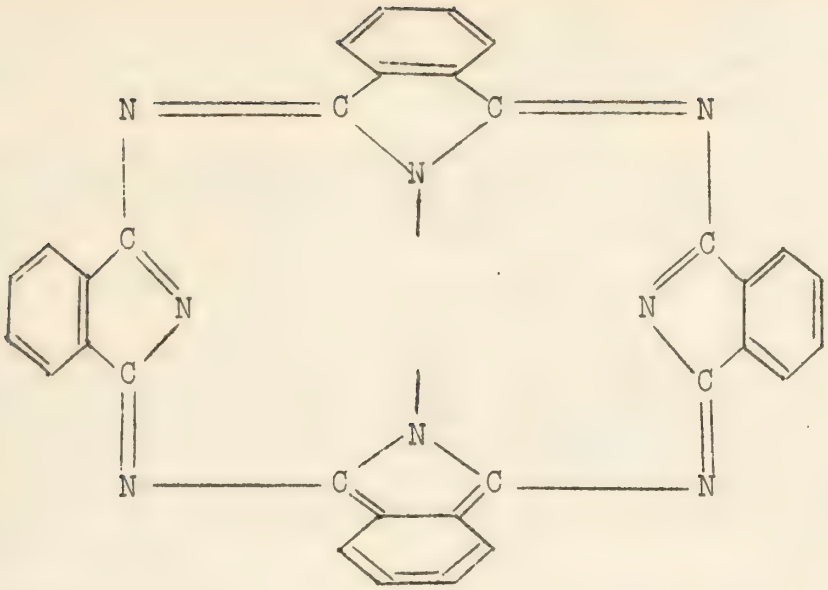
The question of whether phthalocyanin formation is a property of all 1,2-dinitriles has been investigated. All ten possible dicyanonaphthalenes were prepared. Only the 1,2- and 2,3-isomers gave metal-containing pigments of the phthalocyanin type. In the case of heterocyclic rings this matter is more difficult to answer. It was found that:

1. There must be a double bond between the carbons carrying the cyano groups or a bond capable of shifting to this position.

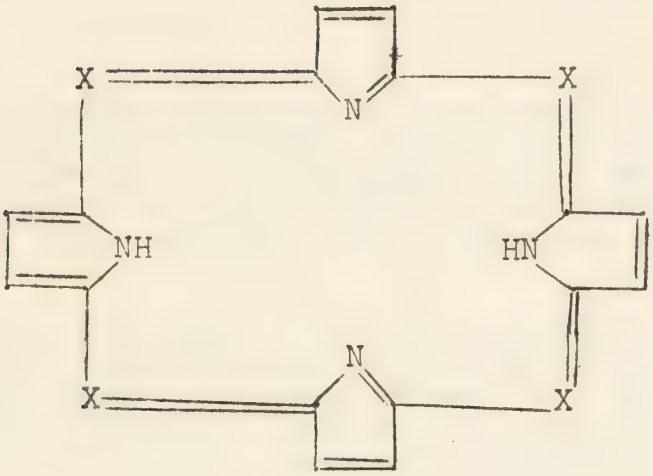
2. The molecule must be quite resistant to decomposition by heat.

3. The geometry of the molecule must be such that the following ring closure can take place:





III



IIIa

Structure.--In 1933 the structure (III) was proposed for phthalocyanin. This formula has had support of many kinds. The best support comes from synthesis, quantitative oxidation, and from the exclusion of other possibilities. The structure consists of four corners with isoindole nuclei that are linked together through nitrogen. Inside the ring there are two imino hydrogens that may be replaced by metal. Consequently the phthalocyanin molecule must be planar. J. M. Robertson confirmed this view by means of X-ray studies.

If copper phthalocyanin is a symmetrical resonance hybrid the copper atom will be held equally by all four isoindole nitrogens. If, however, the single and double bonds are fixed we would expect to get isomers. Isomers have never been found. The same is true of phthalocyanin when it carries only hydrogen.

The preparation of N methyl derivatives has not been possible in spite of a great deal of work to prepare a compound of this type. That this is so undoubtedly follows from the fact that the methyl group cannot attach itself to two nitrogens and hence that resonance is not possible in a dimethyl phthalocyanin.

Properties of Phthalocyanin.--Phthalocyanin can be oxidized with acidic oxidizing agents, the best of which is $Ce(SO_4)_2$ in strong sulfuric acid, which oxidation is quantitative, as follows:

$$(C_8H_4N_2)_4Cu + 3H_2SO_4 + 7H_2O + O \longrightarrow 4C_8H_5O_2N + CuSO_4 + 2(NH_4)_2SO_4$$

It has been shown that phthalocyanin and some of its metallic derivatives possess catalytic activity. Phthalocyanin and copper phthalocyanin are capable of activating hydrogen molecules and of converting para-hydrogen into normal hydrogen. More recently A. H. Cook observed that iron phthalocyanin has catalytic activity similar to that of Haemin and other iron-containing compounds of the porphyrin type.

During this year it has been shown that phthalocyanin compounds of magnesium and other metals of group II when oxidized by means of organic peroxides at 180° give off a powerful red light. A similar effect has been observed in the magnesium and zinc derivatives of other macrocyclic pigments, specifically with chlorophyl.

Several phthalocyanins have found use as pigments in industry. Since the more stable phthalocyanins, Cu phthalocyanin, e.g., are stable to molten potash and boiling HCl acid and since they have a very great covering power and are very insoluble in the ordinary solvents it is only reasonable that they have found commercial application.

Of especial interest is the far-reaching similarity between the structure of phthalocyanin and the natural porphyrins. The formula (IIIa), suggested by Wm. Küster and supported by the work of Hans Fischer, shows how similar the porphyrins are to the phthalocyanin. All these macrocyclic pigments contain four pyrrole rings that are connected by four bridging atoms or groups. Helberger's nomenclature for such rings when at least one connecting group is nitrogen is azaporphin, thus phthalocyanin should be called tetrabenzo tetra-azaporphin.

Linstead expresses the opinion that all these compounds will sooner or later prove to be resonance hybrids without fixed single or double bonds.

Hans Fischer was the first to discover a compound that had both methine and nitrogen bridges and also the first (in 1937) to prepare such an azaporphin. The next step was the preparation of tetrabenz azaporphins which showed still greater similarity with the phthalocyanin. The preparation of compounds in which the four bridge atoms were replaced one by one with methine groups followed. Compounds of this type were first prepared by J. H. Helberger. The methods used for preparing these compounds are quite varied but the products obtained by the various methods seem to be the same. Linstead has prepared all the macrocyclic

pigments except tetrabenz diazaporphin and has proved their structure by quantitative oxidation. These pigments have great similarity but they do show their differences in the way that they react toward oxidizing agents. Thus, when subjected to the oxidizing action of nitric and sulfuric acids they show characteristic colors.

Helberger observed characteristic differences in the stability of the metallic derivatives. Linstead's latest work pertains to the characteristic differences which exist in the various absorption spectra.

"Macrocyclic pigments" are an entirely new class of organic compounds of singular complexity and remarkable symmetry. A wide field for further work in organic, physical, and biological chemistry has thus been opened up.

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Reported by F. C. Dietz
October 11, 1939

ORGANIC FLUORINE COMPOUNDS

Scherer -- I. G. Farbenindustrie A. G.

In recent years organic fluorine compounds have attained considerable importance in industry. Aliphatic chlorofluoro derivatives have entered commerce under the collective name "Freon" as so-called safety refrigerants; fluorine-containing dyestuffs have been put on the market by the I. B. (as well as by du Pont, etc.).

In the aliphatic series the most important synthesis is that of Swarts, who found some fifty years ago that SbF_3 in the presence of $SbCl_5$ could substitute fluorine for chlorine in a large number of chlorinated hydrocarbons. A typical reaction would be:

$$3CCl_4 + SbF_3 = 3CCl_3F + SbCl_3$$

In the aromatic series the presence of $SbCl_5$ is unnecessary.

This synthesis can be simplified and made considerably cheaper by the substitution of anhydrous HF for the SbF_3. A catalyst is still necessary with aliphatic compounds, with only one known exception; this is the reaction of HF with methyl chloroform (CCl_3CH_3) whose constitution is remarkably like that of benzotrichloride.

Other reactions have been studied, but with the following exceptions have found little technical interest.

Substitution of Fluorine for OH.--Important in the preparation of methyl and ethyl fluorides since it is not possible to prepare these from the corresponding chlorides--this would require the use of silver fluoride which is impracticable. In the presence of catalysts HF produces from methyl and ethyl alcohols the corresponding fluorides in very good yields.

Introduction of Fluorine to a Ring.--In the laboratory the method of Schiemann may be used (thermal decomposition of the diazonium borofluorides) but technically a modification has been developed. The proper amine is dissolved in anhydrous HF and diazotized with solid sodium nitrite. Evolution of nitrogen follows without a catalyst merely upon warming. With simple compounds the yield is about 90 per cent.

Addition to Double Bonds.--In the cases studied (propylene, butylene, and higher compounds as oleic acid) HF adds smoothly. In fact, the addition of HF to oleic acid requires much less time for completion than does hydrochloric acid.

Preparation of Other Synthetic Materials.--Through the splitting out of two chlorine atoms from a chlorofluoroethane, trifluorochloroethylene is obtained; this compound gives a colorless polymer which is noninflammable and insoluble in all solvents.

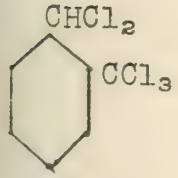
Benzotrifluoride and its derivatives may be nitrated and through reduction may be transformed into the corresponding amines. The diazo compounds of these give valuable colors with naphthol-AS bases. It has been shown that the CF_3 group does not only favorably

influence the fastness to light but also shifts the dye tones toward the yellow.

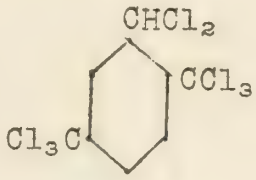
In order to prepare the aromatic trifluormethyl compounds the corresponding chloro derivatives must first be prepared. Benzotrichloride and its derivatives are easily prepared but the complete chlorination of the polymethylbenzenes is more difficult and has not been studied so much. For this reason attention was paid to the factors affecting the completeness of chlorination of the sidechains of a compound such as xylene.

The importance of light in the chlorination of sidechains has been realized for a long time but is commonly much overestimated. Thus, it was observed that in the complete absence of all illumination the rate of reaction is one-half that of a condition of strong illumination. There is also little difference in the effect of ultraviolet light and that of the visible spectrum (in which the absorption lines of chlorine lie). Much greater acceleration of the reaction is brought about by the increase of the partial pressure of the chlorine. With a 10 per cent excess of chlorine the chlorination of xylene required thirty hours; with a 3- to 4-times excess the reaction can be finished in eight to ten hours. Thus, the partial pressure of the chlorine clearly determines the speed of the reaction.

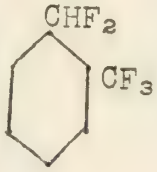
All of the hydrogen atoms of the sidechains of meta- and para-xylenes and of mesitylene may be replaced by chlorine. However, ortho-xylene and pseudocumene behave quite differently. Due to steric hindrance it is impossible to replace more than 5 or 8 hydrogen atoms respectively. The compounds produced are I and II below. These may be transformed into the corresponding fluoro derivatives by means of HF, an unexpected reaction, since only resinous products result from the action of HF on benzal chloride. Compounds produced are III and IV below.



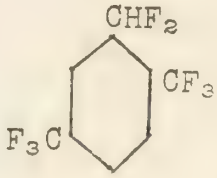
I



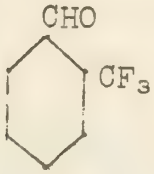
II



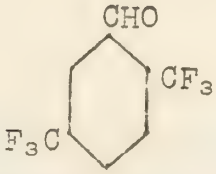
III



IV



V

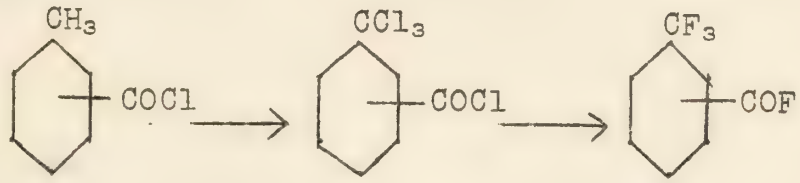


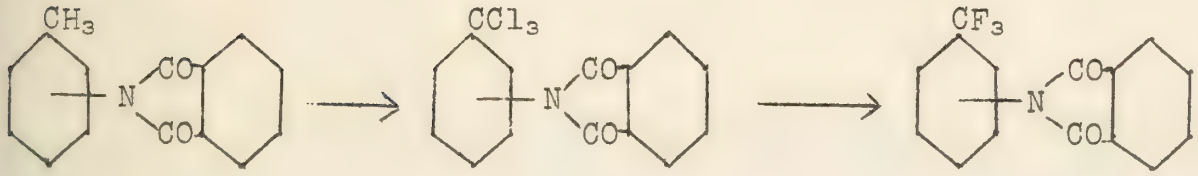
VI

These benzalfluorides may be hydrolyzed to trifluoromethyl substituted benzaldehydes by the action of concentrated sulfuric acid; previously by the usual methods trifluoromethyl benzenes could not be transformed to aldehydes. Products formed are V and VI above.

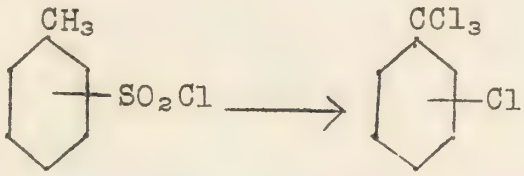
As noted above steric hindrance was believed to prevent complete replacement of hydrogen on adjacent sidechains by chlorine. It was surmised that after the chlorine atoms were replaced by the smaller fluorine atoms there might be enough room so that the last hydrogen atom could now be replaced by chlorine; this was investigated and found to be the case. Of course, this chlorine atom could now be replaced by fluorine as before resulting in 1,2-bis-trifluoromethylbenzene in the case of o-xylene for example.

In respect to the influence of substituents upon chlorination and fluorination of methyl benzenes it may be said that in most cases halogenation is hindered. Besides chlorine only the carbonyl and phthalimid groups allow a high degree of halogenation, for example:

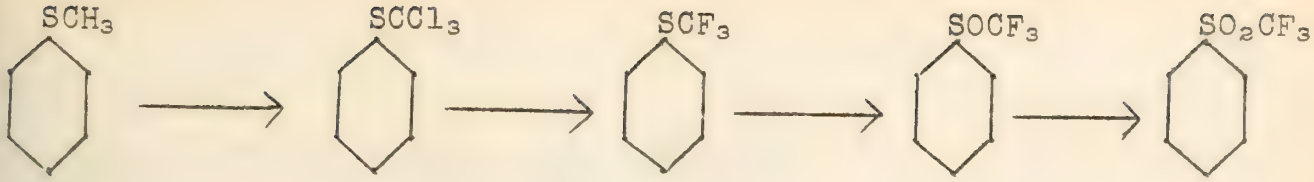




Other substituents studied hinder either chlorination or fluorination. For example, tolunitrile may be made into trichloromethyl benzonitrile but cannot be further fluorinated; nitrotoluene cannot be completely chlorinated, nitrobenzalchloride being produced under favorable conditions. In the case of toluene sulfonyl chloride the SO_2Cl group is split off and replaced by chlorine as follows:

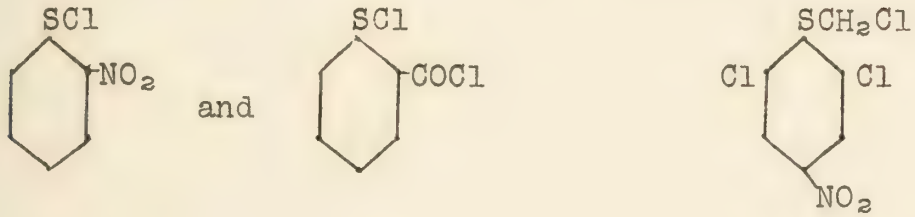


Two other classes of aromatic fluorine compounds may be mentioned, one whose CF_3 group is not directly attached to the benzene ring. In the first, trichloromethylphenyl sulfide, the chlorine atoms may easily be replaced by fluorine with formation of trifluoromethylphenyl sulfide:



In contrast to the case of the methyl benzenes, here the benzene nucleus may contain any of several substituents, for example, chloromethyl, carboxyl and nitro groups, so that the reaction is not limited to the simple trifluoromethylphenyl sulfide.

This class of compounds is quite stable; they may be nitrated or chlorinated. Upon oxidation either the corresponding sulfoxide or sulfone is produced. Here, however, there are several exceptions. If a meta-directing group is ortho to the methyl sulfide group a derivative of phenylthiochloride is obtained by splitting out of the methyl group, for example, I and II below:



I II III

If the methyl sulfide group is flanked by two substituents then only one chlorine atom will enter the sidechain. Thus, from 2,6-dichloro-4-nitrophenylmethyl sulfide one gets derivative III above. This behavior seems unexpected because 2,6-dichlorotoluene may be chlorinated to a benzalchloride. This steric hindrance probably arises from the valence angle of the sulfur.

In the second class of compounds, the sulfonyl fluorides, the fluorine atom is marked by unusual stability. These compounds are much more resistant to hydrolysis or reduction than are the corresponding chlorides so that under conditions in which the latter would be rapidly reduced to thiols the fluorides are left untouched. They can be nitrated without loss of the SO_2F group, the nitro group reduced to an amino group which may then be diazotized in acid solution and the diazonium solution subjected to the usual reactions, such as reduction, the Sandmeyer reaction, or decomposition by iodides--all without loss of the sulfonyl fluoride group. To alcohol they are indifferent; only when alkalies are added do the esters of the sulfonic acids form. Aromatic bases such as aniline do not react with the sulfonyl fluorides of hydrocarbons; primary and secondary aliphatic bases react rapidly to form mono- or dialkylated sulfamides. Aqueous ammonia slowly transforms the sulfonyl fluorides into amides but a part is hydrolyzed and forms the ammonium salt of the corresponding sulfonic acid so that a better yield of the amide results from reaction with ammonia under increased temperature and pressure.

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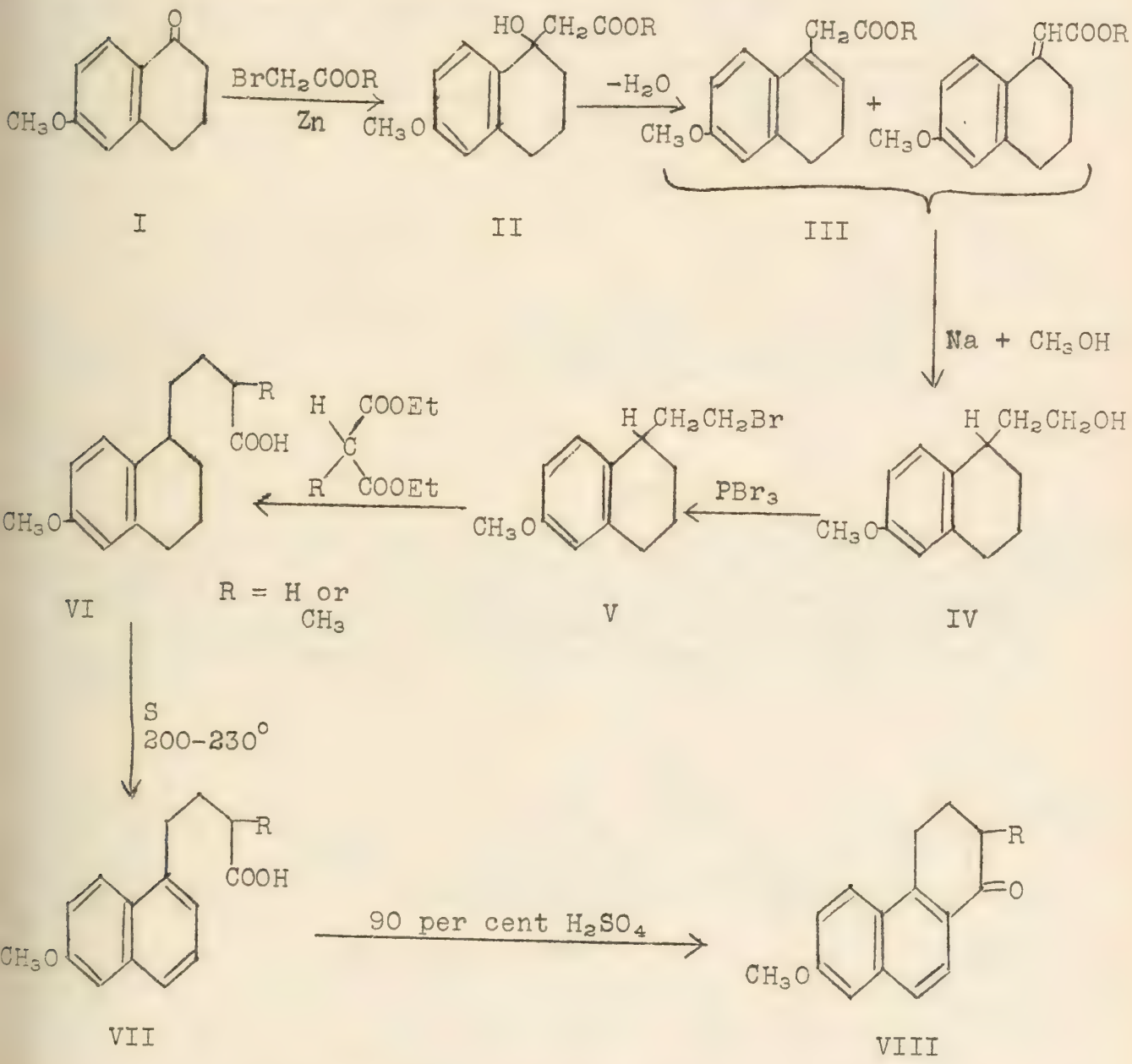
Reported by L. Wakefield
October 18, 1939.

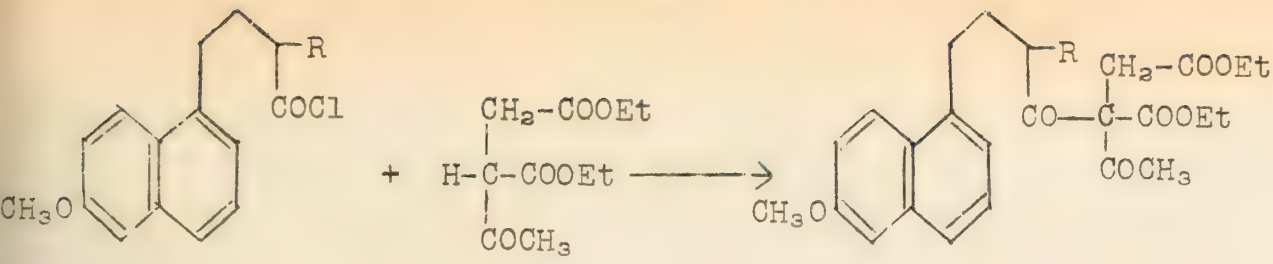
THE SYNTHESIS OF NATURAL STEROLS

Haberland -- University of Breslau
Bachmann, Cole, and Wilds -- University of Michigan

A recent method for synthesizing natural sterols has been worked out by Haberland using a partially hydrogenated phenanthrene derivative as the starting material. He synthesized 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene as follows:

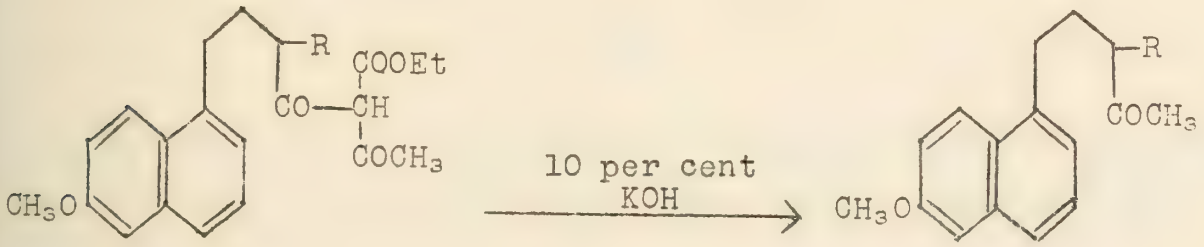


The next step involved the formation of a five-membered ring on the phenanthrene skeleton. Haberland first attempted to do this by condensing the acid chloride of VII with acetosuccinic ester.



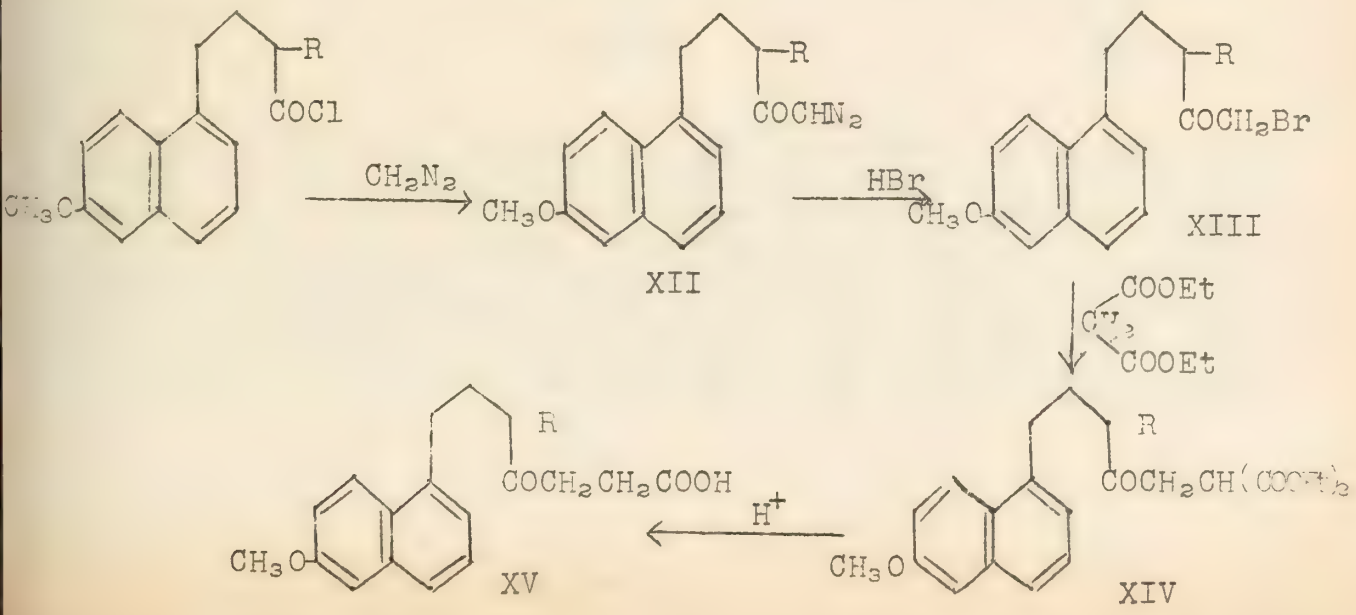
IX

However, he was unable to cleave IX to the corresponding keto acid as was reported by Chang-Kong Chuang. In all cases the acid (VII) was obtained. In order to determine if this acid would behave in a similar manner with other β-diketo carboxylic esters, it was condensed with acetoacetic ester. The condensation product (X) could be cleaved with dilute sodium hydroxide to give the expected ketone (XI).



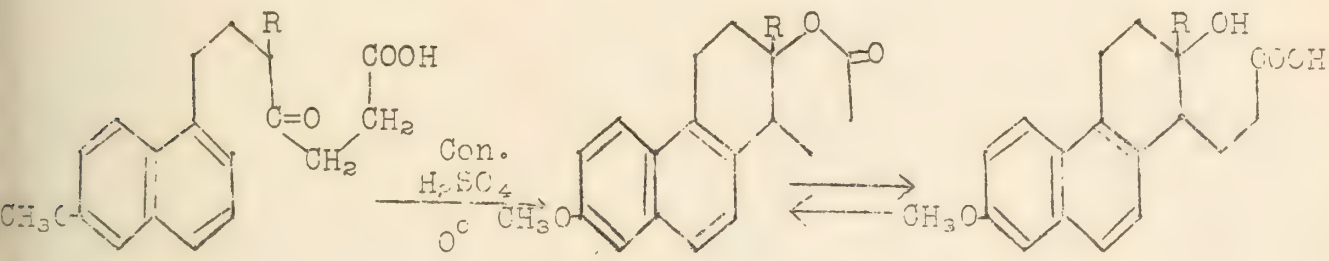
X XI

Since the keto acid synthesis failed, the following procedure was devised: The chloride of acid (VII) on treatment with diazomethane gives the diazoketone (XII) which is easily converted to the bromoketone (XIII) by hydrobromic acid. By means of the malonic ester synthesis the desired keto acid (XV) can now be prepared.



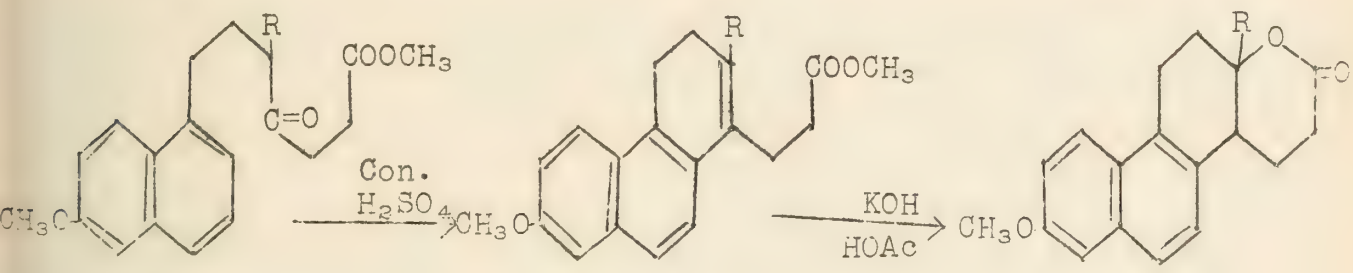
XII XIII XIV XV

When R = H, the above series of reactions proceeds less smoothly and the yields are lower than when R = CH_3. The free acid (XV) gives a lactone (XVI) when treated with concentrated sulfuric acid. The lactone can be split with dilute sodium hydroxide and under careful conditions the free tetrahydrohydroxyphenanthrene acid (XVII) can be obtained. However, by warming or by treatment with dilute mineral acids the hydroxy acid (XVII) readily goes back to the lactone (XVI).



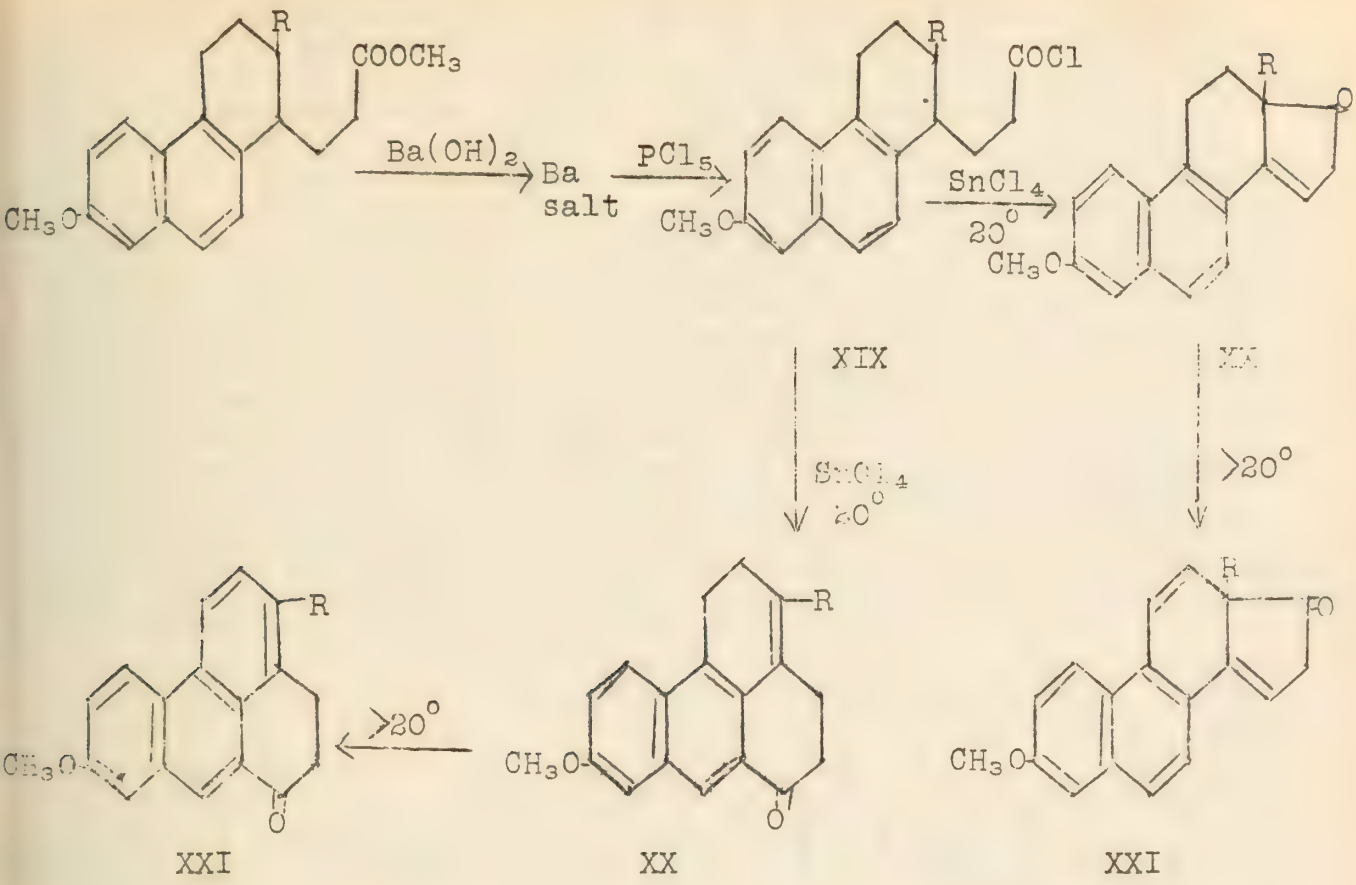
XV XVI XVII

If the ester of XV is treated with sulfuric acid, one obtains a dihydrophenanthrene propionic ester (XVIII). The corresponding free acid could not be obtained. Upon saponification of the ester (XVIII) and treatment with acetic acid the lactone (XVI) results.

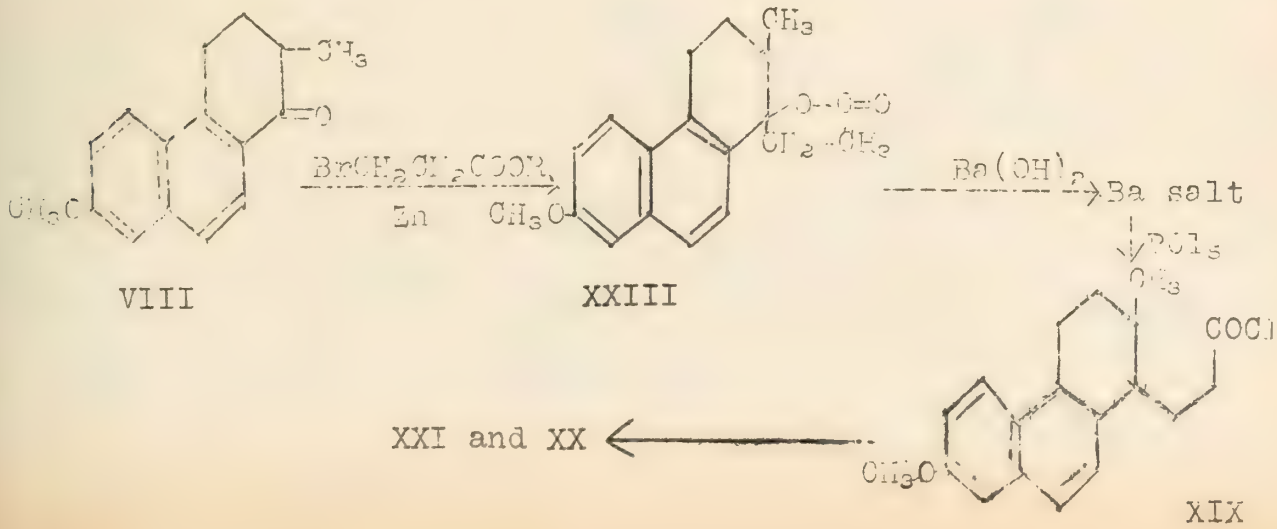


XVIII XVI

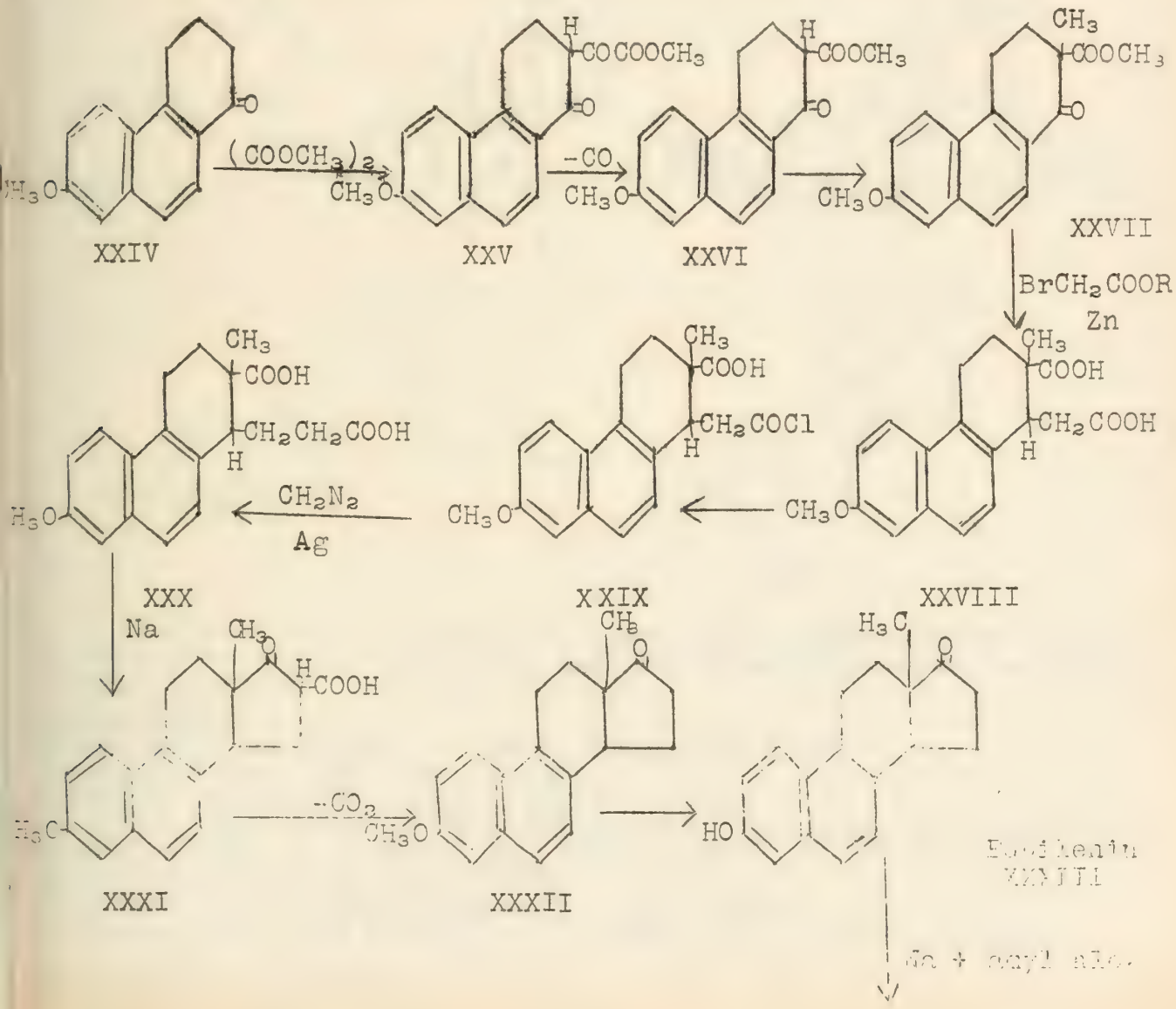
The tetracyclic ketone (XX) can be prepared both from ester (XVIII) and the lactone (XVI). The acid chloride (XIX) is prepared by way of the barium salt from the ester (XVIII). This, upon treatment with stannic chloride at 20° C., gives a colorless ketone $C_{19}H_{18}O_2$ (XX). If the ring closure is carried out at higher temperatures one obtains a yellow ketone $C_{19}H_{16}O_2$ (XXI). Since ring closure can take place in either of two rings, it seems likely that either ketone XX or XXI must be the desired product.

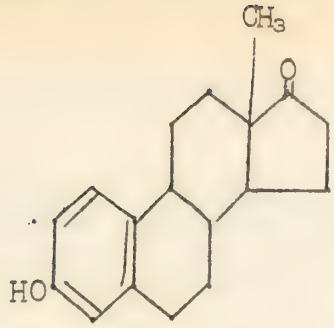


Haberland and Heinrich have worked out a second method of sterol synthesis by employing the Reformatzky reaction. The ketone (VIII) is condensed with α-bromopropionic ester. The reaction proceeds smoothly, producing a lactone $C_{19}H_{20}O_3$ (XXIII) which is not identical with the above lactone (XVI). Haberland thus assigned a spiro structure to the lactone (XXIII). Upon treating this lactone with barium hydroxide, then phosphorous pentachloride, one obtains the acid chloride (XIX) from which the tetracyclic ketones (XX and XXI) can be prepared by treatment with stannic chloride as previously described.



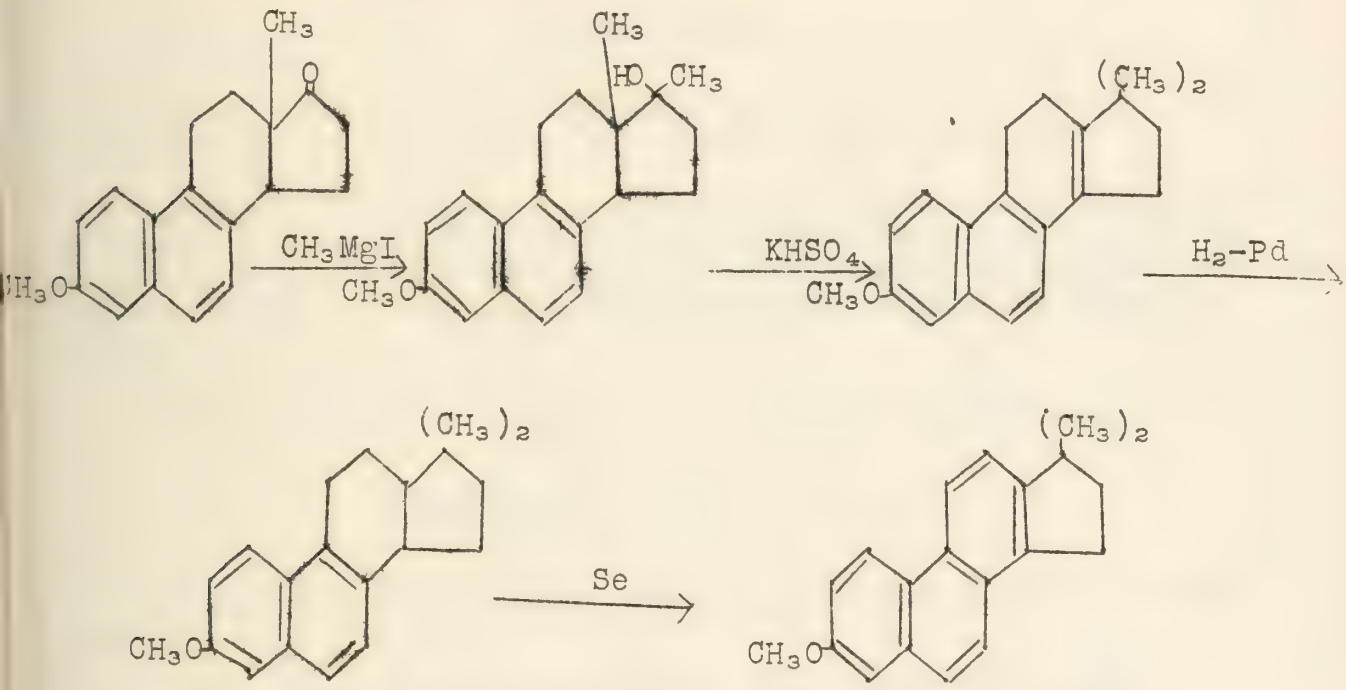
Bachmann, Cole, and Wilds have recently reported the total synthesis of equilenin. Since Marker succeeded in converting equilenin to estrone by reduction, the method also offers a synthesis of estrone. The starting point was 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene (XXIV). This was condensed with methyl oxalate to give the 1-keto-2-glyoxalate derivative (XXV) which gives the carbomethoxy derivative (III) by elimination of carbon monoxide. Methylation of XXVI gives 7-methoxy-1-keto-2-methyl-2-carbomethoxy tetrahydrophenanthrene (XXVII). To build up the five-membered ring the Reformatzky reaction was used, followed by dehydration and reduction of the unsaturated acid to give XXVIII. Compound XXVIII consisted of two racemic mixtures which were separated into cis-(m.p. 228-230°) and trans- (m.p. 208-210°)-7-methoxy-1-acetic acid-2-methyl-2-carboxy tetrahydrophenanthrene. Each of these acids was converted to the acid chloride (XXIX) which upon treatment with diazomethane gave XXX. The dimethyl ester of trans-7-methoxy-1-propionic acid-2-methyl-2-carboxy tetrahydrophenanthrene was cyclized by sodium and the product converted to dl-equilenin by the usual hydrolysis and decarboxylation including hydrolysis of the methoxy group. Synthetic equilenin, m.p. 265-267°; natural equilenin, m.p. 258°.





Estrone
XXXIV

The structure of synthetic equilenin was definitely established by conversion to 3',3'-dimethyl-7-methoxy-1,2-cyclopentenophenanthrene (XXXV) identical with the compound obtained from natural equilenin by Cohen, Cook, and Hewett.



XXXV

The synthetic equilenin was resolved by conversion to the *l*-methoxy acetic ester identical with the *l*-methoxy acetic ester of natural equilenin, m.p. 172-174°.

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Reported by R. W. Upson
October 18, 1939

PREPARATION OF α-HYDROXY ALDEHYDES

Freon -- The Sorbonne (Paris University)

The α-hydroxy aldehydes are not very well known and are difficult to prepare. About a dozen have been synthesized by methods which give either poor yields or require difficultly obtainable starting compounds. Five have contained tertiary hydroxyl groups.

Freon first tried to prepare the α-hydroxy aldehydes containing a tertiary hydroxyl group by using as starting materials methyl glyoxal dimethyl monoacetal [$CH_3COCH(OCH_3)_2$], or the corresponding higher alkyl derivatives. The series of reactions proposed follows:

$$RCOCH(OCH_3)_2 + R'MgX \longrightarrow RC(OH)(R')CH(OCH_3)_2 \xrightarrow{H_2O}$$

$$RC(OH)(R')CHO$$

The yields (1-2 per cent) obtained in the formation of the glyoxal acetals were so small that this method was abandoned.

Successful syntheses of α-hydroxy aldehydes and α-hydroxyketones result from the treatment of α-nitrosoketones with the Grignard reagent, and hydrolysis of the resulting tertiary hydroxyoximes to the corresponding α-hydroxy aldehydes, or α-hydroxyketones.

$$RCOCH(R')=NOH + R''MgX \longrightarrow RC(OH)(R'')C(R')=NOH$$

$$\xrightarrow{\text{hydrolysis}} RC(OH)(R'')C(R')=O$$

The α-isonitrosoketones treated with the Grignard reagent were:

(1) Isonitrosomethylethylketone: $CH_3COC(CH_3)=NOH$

(2) Isonitrosoacetone: $CH_3COCH=NOH$

(3) Isonitrosoacetophenone: $C_6H_5COCH=NOH$

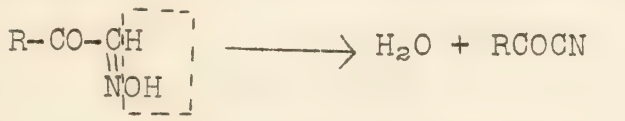
Hydrolysis of the α-hydroxyoximes thus obtained constitutes a good method of preparation of the α-hydroxyketones: $CH_3C(OH)(R)COCH_3$ and $CH_3C(OH)(Ar)COCH_3$; α-hydroxy aldehydes: $CH_3C(OH)(R)CHO$, $CH_3C(OH)(Ar)CHO$, $C_6H_5C(OH)(R)CHO$ and $C_6H_5C(OH)(Ar)CHO$.

The Grignard reaction proceeds normally in the case of the isonitrosomethylethylketone [$CH_3COC(CH_3)=NOH$]; yield, 57-83 per cent).

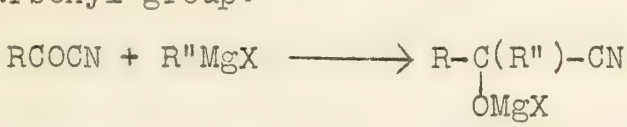
With the isonitrosoketones of the form $RCOCH=NOH$, a secondary reaction resulting in the formation of a ketone, reduces the yield

of the α-hydroxy aldoxime to about 36-50 per cent. The mechanism which has been proposed for this secondary reaction is as follows:

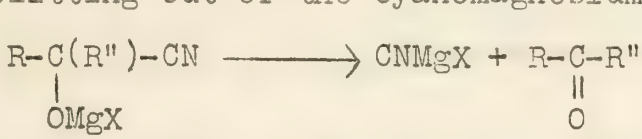
(1) Dehydration of the oxime group.



(2) Reaction of the Grignard reagent with the carbonyl group.



(3) Splitting out of the cyanomagnesium halide.



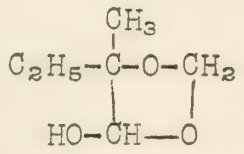
This mechanism explains the presence of the ketone RCOR", and also (sometimes observed) the tertiary alcohol $RC(OH)=R")_2$, which can be formed from the ketone. The isonitrosoketones of the form RCOC(R')=NOH do not give this secondary reaction because the dehydration of the oxime is no longer possible. The formation of the ketone has been observed only when at least one of the two radicals R and R" (of the isonitrosoketone and the Grignard reagent) is an aliphatic group. When R and R" are both aliphatic, the formation of the hydroxyoxime is still the predominant reaction.

Isonitrosoacetophenone ($C_6H_5COCH=NOH$) gives yields of α-hydroxy aldoximes from 50-65 per cent. Again, the ketone is formed only if the Grignard reagent is aliphatic.

The α-hydroxy aldoximes and α-hydroxyketoximes are usually very viscous liquids which may be distilled under 2-3 mm. pressure with decomposition in several cases.

Hydrolysis of the α-hydroxyoximes in order to obtain the corresponding α-hydroxy aldehydes and α-hydroxyketones has been carried out by means of dilute acid (hydrochloric, sulfuric, oxalic), or by means of formaldehyde (35 per cent) and concentrated hydrochloric acid. The yields of the α-hydroxy aldehydes are always lower than of the α-hydroxyketones; the lower molecular weight compounds of the α-hydroxy aldehydes can be obtained in only very small amounts. The stability of the α-hydroxy aldehydes increases with an increase in their molecular weight.

Hydrolysis of the methylethylglycol aldoxime [$CH_3C(OH)(C_2H_5)CH=NOH$] does not give the monomeric α-hydroxy aldehyde; using oxalic acid or sulfuric acid for hydrolysis the ethylene aldehyde ($CH_3CH=C(CH_3)CHO$) is obtained due to dehydration. Hydrolysis by formaldehyde (35 per cent) and concentrated hydrochloric acid gives an addition product of formaldehyde with the methylethylglycol aldehyde, for which the following structure has been proposed.



This product is accompanied by a small quantity of the dimer of the desired α-hydroxy aldehyde $(C_5H_{10}O_2)_2$.

If, in general, the oximes are liquid and distil with decomposition, it is advantageous, in order to improve the yields, to hydrolyze the crude products from the Grignard reaction without isolating the hydroxyoximes by distillation. The overall yields are generally about 50-70 per cent.

Most of the α-hydroxy aldehydes and α-hydroxyketones are quite stable compounds. Oximes and semicarbazones may be obtained. The α-hydroxy aldehydes of the aliphatic series dehydrate readily, especially the lower members of the series. The methylethylglycol aldehyde (at least in the monomeric state) cannot be isolated. The methylbutylglycol aldehyde is obtained, accompanied by a considerable portion of the ethylene aldehyde arising from the partial dehydration. The aromatic α-hydroxyketones and the aliphatic or aromatic α-hydroxyketones form stable acetates.

In conclusion, α-hydroxy aldehydes (except the low molecular weight aliphatic α-hydroxy aldehydes) and α-hydroxyketones containing a tertiary hydroxyl group can be synthesized by treatment of α-nitrosoketones with the Grignard reagent, and hydrolysis of the resulting tertiary hydroxyoximes. The α-hydroxy aldehydes and α-hydroxyketones are all stable compounds except the low molecular weight aliphatic α-hydroxy aldehydes which dehydrate easily.

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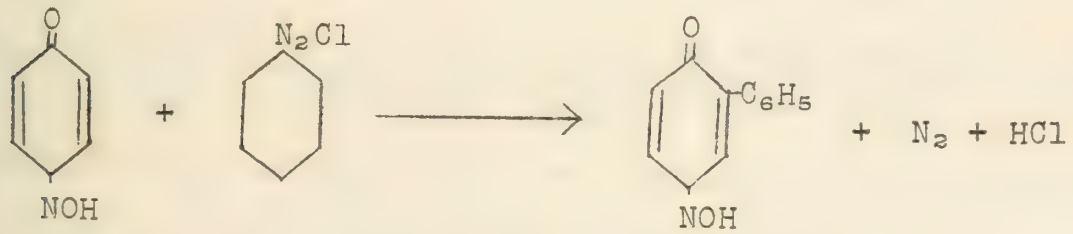
Reported by L. B. Poland
October 25, 1939.

THE REACTION OF AROMATIC DIAZO COMPOUNDS ON α,β-UNSATURATED CARBONYL COMPOUNDS

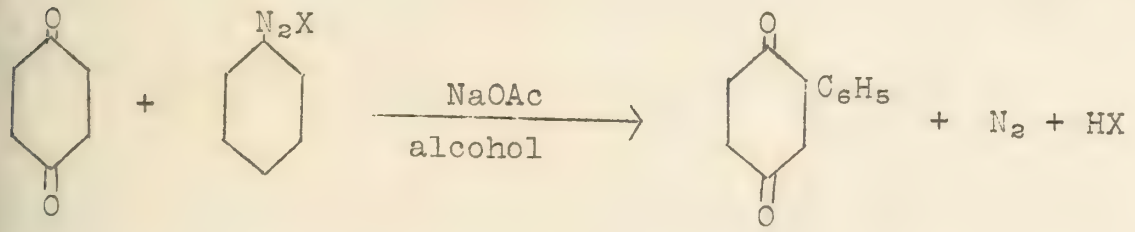
Meerwein -- University of Marburg

The coupling process of aromatic diazo compounds depends upon the discovery by K. H. Meyer in 1913 that diazo compounds add to the double bond of properly substituted aromatic compounds. He extended his investigations to show that a similar reaction could take place with unsaturated aliphatic hydrocarbons which possessed sufficiently reactive double bonds. In all of the cases explained, the final product was an azo compound.

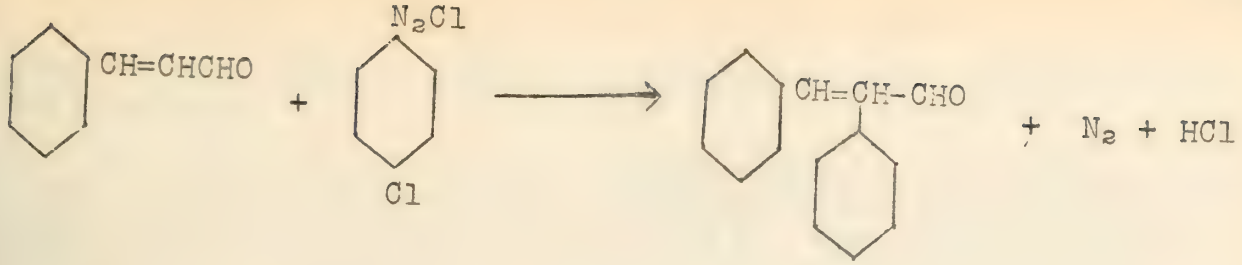
Since α,β-unsaturated carbonyl compounds show a great tendency for different types of addition reactions, one might expect them to react with aromatic diazo compounds. A patented process for the oxidation of propenyl benzene derivatives by the use of aromatic diazo compounds has been described. This leads to a phenylhydrazone of the aromatic aldehyde which has been formed. Boesche made the interesting discovery that benzene diazonium chloride reacts with para-nitrosophenol to give a phenylated nitrosophenol instead of an azo compound.



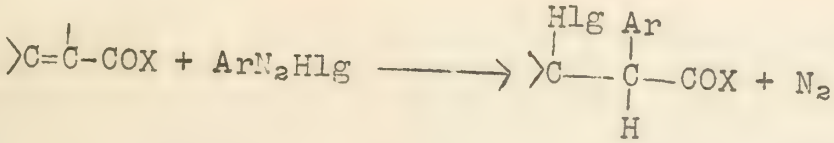
A reaction closely akin to this has been recently reported in the patent literature.



Meerwein has extended the reaction to other α,β-unsaturated carbonyl compounds and has found that the reaction is quite general. Here, however, no azo compounds are formed, but nitrogen is split off quantitatively and an α-arylated compound is obtained. Thus cinnamic aldehyde and p-chlorobenzene diazonium chloride yield α-(p-chlorophenyl)-cinnamic aldehyde.

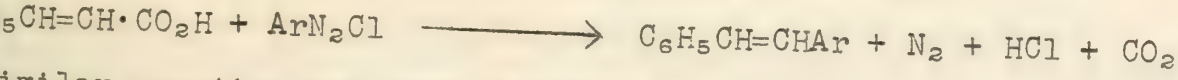


In some cases a product is obtained which is formed by the addition of the eliminated hydrogen halide to the α-arylated carbonyl compound.



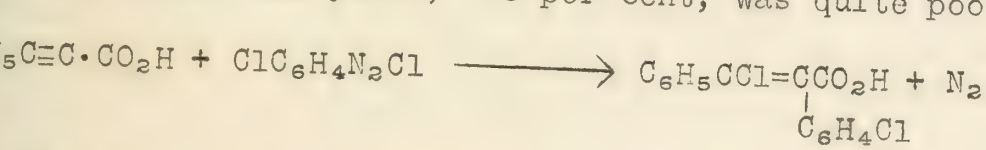
Maleic and fumaric esters react with p-chlorobenzene diazonium chloride to yield the two stereoisomeric forms of α-(p-chlorophenyl)-β-chlorotartaric esters.

Cinnamic acid shows a somewhat irregular behavior in that the carboxyl group is split off as carbon dioxide so that, in place of the α-arylated cinnamic acid, stilbenes are obtained.



A similar reaction has been observed with crotonic acid.

Acetylenic compounds have been shown to behave like the double bonded hydrocarbons. Phenylpropiolic acid reacted with p-chlorobenzene diazonium chloride to give α-(p-chlorophenyl)-β-chlorocinnamic acid. The yield, 7.8 per cent, was quite poor.



The reaction of the diazo compound with α,β-unsaturated carbonyl compound is carried out in weak mineral acid, acetic acid or chloroacetic acid solution with the addition of sodium acetate, pyridine acetate, or the alkali salts of other weak acids. The reaction mixture is usually diluted with an equal volume of acetone in order to produce a more homogeneous mixture. Besides this, acetone seems to produce a specific effect. Other water soluble solvents such as alcohol and dioxane are useless. Cupric salts catalyze the reaction considerably whereas cuprous salts seem to have little or no effect. The reaction is carried out between 5° and 40°C. depending upon the specific reactants and the acidity of the solution. The reaction takes place in general only with diazonium chlorides and bromides. The sulfates and nitrates

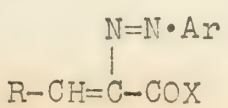
either do not react or produce considerably poorer yields and impure products.

The yields of addition or arylated product are satisfactory only in a relatively few cases. Cinnamonitrile and p-chlorobenzene diazonium chloride give a 76.5 per cent yield of α-(p-chlorophenyl)-cinnamonitrile. On the other hand, the yields of the products obtained from p-chlorobenzene diazonium chloride and p-chlorobenzene diazonium bromide with methyl cinnamate are only 30 and 26.3 per cent, respectively. Crotonic acid and p-nitrobenzene diazonium chloride produce only 6.8 per cent of α,β-nitrophenylcrotonic acid.

In general, the yield depends very markedly upon the nature of the diazo compound. From the experiments so far carried out it can be assumed that negative substituents such as -Cl, $-NO_2$, $-CO_2H$, and $-SO_3Na$ in the para position to the diazonium group influence the yield favorably. Similar groups in the ortho position produce a less favorable yield due supposedly to steric hindrance. The influence of substituents in the benzene nucleus of the α,β-unsaturated carbonyl compounds, such as cinnamic acid, has only been very incompletely investigated. It has been found that most of the substituted cinnamic acids do not react or react very slowly with the diazo compounds because of their low solubility. The pH of the solvent is also of importance in influencing the course of the reaction. In alkaline solution, the normal coupling reaction takes place to produce azo dyes; in sufficiently acid solution the arylation process takes place. The degree of acidity must be determined for each specific reaction.

In spite of low yields the described process possesses a general preparative interest. The yields given in all cases depend upon the use of equimolecular quantities of reactants. By the use of excess diazo compound, the yield can be increased considerably. Thus the yield of 3,p-chlorophenylcumarin was raised from 45.6 per cent to 56.1 per cent by employing 1.5 moles of the diazo compound to one mole of the cumarin. The poor yields of arylated products are produced through a series of side reactions. Halobenzenes arise in small amounts as products of a normal Sandmeyer reaction. The most disturbing influence is the formation of the so-called diazo resins about whose nature and mechanism of formation nothing is known. A third side reaction arises from the reaction of the diazonium halide upon the acetone which has been used as a solvent.

Meerwein has postulated a reaction mechanism for the reaction of diazo compounds upon α,β-unsaturated carbonyl compounds. He is of the opinion that the formation of any nitrogen-containing intermediate products is very unlikely. Azo compounds of type I or II show no tendency to decompose spontaneously with the loss of nitrogen.



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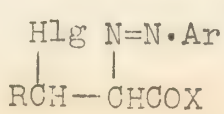
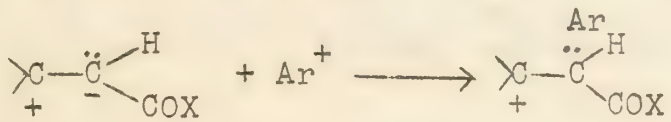


II

A 1,4-addition of the diazo compound can be excluded since unsaturated hydrocarbons react in the same manner as the α,β-unsaturated carbonyl compounds with diazo compounds.

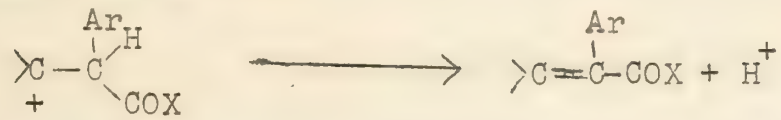
It, therefore, must be assumed that the first step of the reaction depends upon a decomposition of the diazonium ion into nitrogen and an aryl ion. The breakdown of the diazo compound is favored by the presence of the α,β-unsaturated carbonyl compound by negative groups (NO_2, halogen, carbonyl) in the <u>para</u> position to the diazo group, and by the polarizability of the anions. The catalytic effect of cupric salts upon the reactions remains at present unexplained.

The aryl cation formed by the decomposition of the diazonium ion adds to the polarized double bond to complete its octet.

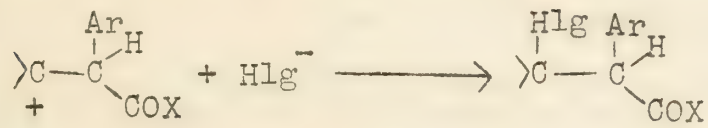


The cation thus formed can stabilize itself in three ways:

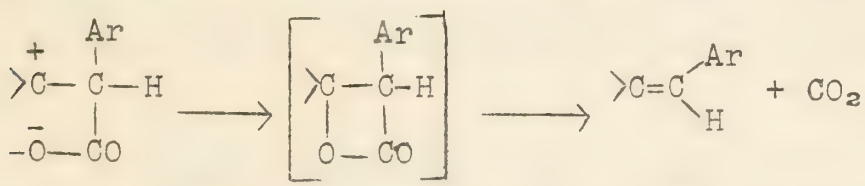
1. Through the loss of a proton and the reformation of the carbon double bond.



2. Through taking up of a halogen ion.



3. In the case of α,β-unsaturated acids through an intramolecular saturation with the carboxylate anion to form an unstable β-lactone which immediately decomposes into CO_2 and an unsaturated hydrocarbon.



An ionic mechanism permits the different observed reaction rates to be explained in a consistent manner.

The previously mentioned side reaction of the diazonium halide with acetone was further investigated. The acetone is changed to monochloroacetone or monobromoacetone while the diazo compound is reduced to the corresponding benzene derivative.

$$ArN_2Hlg + CH_3COCH_3 = CH_3COCH_2Hlg + ArH + N_2$$

Meerwein and his associates have extended the study of the reaction to a quantitative determination of the amount of monochloro- or monobromoacetone produced. The simultaneously formed benzene derivatives have only been isolated in a few cases. The yield of monochloroacetone from p-chlorobenzene diazonium chloride and acetone varied from 14.3 to 44.6 per cent depending upon the experimental conditions. Negative substituents in the benzene ring of the diazo compound favor the formation of chloroacetone while positive substituents decrease the yield considerably. By the use of o,p-dichlorobenzene diazonium chloride a yield of 64.8 per cent of chloroacetone was obtained.

The same factors which favor the arylation of α,β-unsaturated carbonyls also increase the yield of halogen acetone. The question of whether the reaction is also ionic or one of neutral radicals cannot be differentiated on the basis of the experiments carried out. The interesting investigations of Waters concerning the formation of free radicals by the reaction of solid benzene diazonium chloride on organic solvents speaks for the latter conception.

Meerwein has found that many diazonium salts dissolve readily in liquid sulfur dioxide to give solutions which show a series of remarkable changes. By heating a solution of p-chlorobenzene diazonium chloride in sulfur dioxide in the presence of anhydrous cupric chloride, an 80 per cent yield of p-chlorobenzene sulfonyl chloride is obtained.

$$\text{p-}ClC_6H_4N_2Cl + SO_2 \longrightarrow \text{p-}ClC_6H_4SO_2Cl + N_2$$

The decomposition of the same diazonium salt with sodium acetate in the absence of cupric chloride produces an azosulfone.

$$\text{p-}ClC_6H_4N_2Cl + SO_2 \longrightarrow \text{p-}ClC_6H_4N{=}NSO_2C_6H_4Cl\text{-p}$$

The acetoxyl radical formed at the same time oxidized a part of the sulfur dioxide to sulfur trioxide whereby it was seemingly changed to acetic anhydride.

$$2CH_3COO + SO_2 = (CH_3CO)_2O + SO_3$$

It is hoped that further investigation of diazonium salts in liquid sulfur dioxide may throw more light upon the question of the formation of free radicals in the splitting of diazonium salts.

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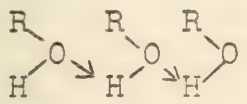
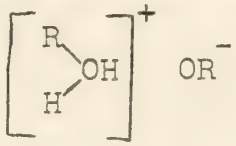
Reported by N. Rabjohn
October 25, 1939.

HYDROGEN BONDING IN ORGANIC COMPOUNDS

The existence of hydrogen bonds in inorganic and organic compounds has now been proven by a wealth of physical data, for example, Raman and infrared spectra, dipole moments, x-ray studies, conductivity, cryoscopic, vapor density measurements, etc. The idea of hydrogen bridging emanated from the properties of simple substances, which had been vaguely attributed to various causes but are now readily explained by this theory. For example, the abnormal freezing point depressions of alcohols in nonpolar solvents is caused by polymerization of the alcohol molecules,



etc. or



I

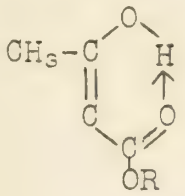
Other familiar cases of association are the fatty acids, benzoic acid, alcohols, hydrocyanic acid, α- and β-oxalic acids, etc.

In 1913 Pfeiffer introduced the concept of hydrogen bonding into organic chemistry and since that time the idea has been used to account for some deviations from some expected physical properties of certain organic compounds. Until recently investigations had centered mainly on physical properties rather than on chemical properties.

Huggins has listed the following types of hydrogen bonds which may occur in organic compounds:

$$OH \leftarrow O,\ OH \leftarrow N,\ NH \leftarrow N,\ CH \leftarrow N,\ CH \leftarrow O,\ OH \leftarrow X$$

Of special interest in organic chemistry is the hydrogen bridging within the molecule. Typical are the chelated acetoacetic ester and acetyl acetone wherein the enol and keto form differ markedly in properties.



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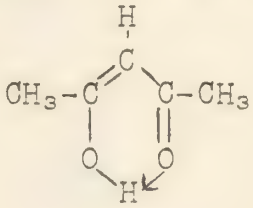


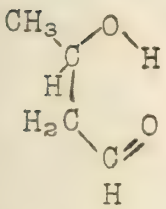
III

The investigation of a large number of organic compounds has shown that the following factors are important in the formation of a chelate ring.

(1) First, there must be a general geometrical possibility for the formation of a stable ring. The most important are the six-membered rings but a seven-membered ring in derritol is known; also there are several examples of five-membered rings such as o-chlorophenol but the hydrogen bridges here are extremely weak.

(2) The intramolecular hydrogen bond is favored if the ring contains a conjugated system which is thereby stabilized by resonance.

The failure to find six-membered rings in compounds such as aldol tartaric esters, benzil monoxime, etc., may be attributed to any one or more of the following factors: insufficient rigidity in the rings, insufficient resonance, insufficient electron affinity of the hydroxyl oxygen, insufficient negativity of the O or N atom on the weak side of the hypothetical bridge or due to repulsion between groups and making the O ⟶ H bridge distance too large.



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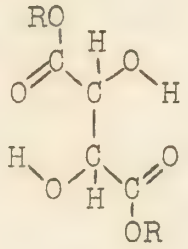

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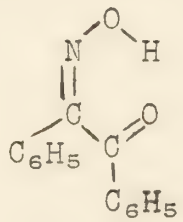
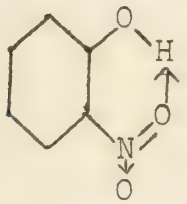


VI

By comparison of the o, m, p-isomers of the benzene series, a far reaching similarity is observed for the m- and p-compounds but the o-compounds differ considerably. Such anomalous properties always occur if in the o-position to an OH group, is a CO, NO_2, NO or -N=N- group and generally if there is a possibility for the formation of intramolecular hydrogen bond as shown in the case of o-nitrophenol.



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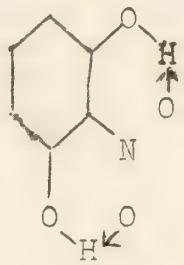
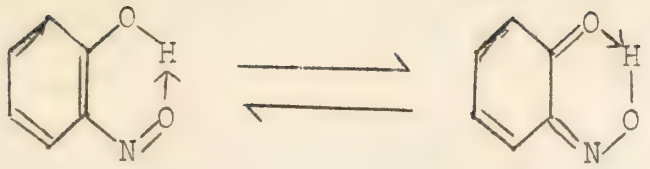


VIII

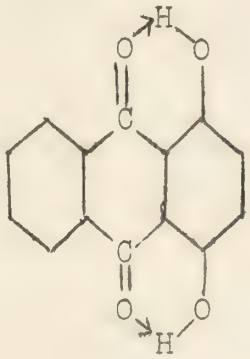
While the methyl ethers of the nitrophenols have very similar properties, the o-nitrophenol has a very much lower boiling point than the m- and p-compounds and is exceptional in that it is volatile with steam. In addition the solubility of these compounds in water and petroleum ether fall in line with their structure. Also, in the case of o-nitrosophenol an intramolecular hydrogen bridge is assumed. On account of resonance relationships two formulas may be written, settling a disputed question as to the structure. Both methods of writing are characteristic of this compound.



IX X

Intramolecular hydrogen bridges with the oxygen of the neighboring CO group occur frequently, for example, salicylaldehyde, salicylic acid amid, o-hydroxyacetophenone, naphthazarin and quinizarin.

XI



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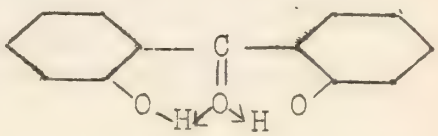
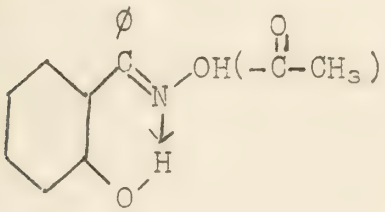


XIII

Hydrogen bridging to nitrogen compounds has been accepted, for example, in salicylaldehyde anil and salicylaldehyde oxime. The determination of chelation in compounds of this kind also determines its stereochemical character. Meisenheimer proved the configuration of syn- and anti-forms by chemical conversion, but also here configuration is determined by lack of OH absorption. These findings stand in agreement with the results of the Beckman rearrangement.



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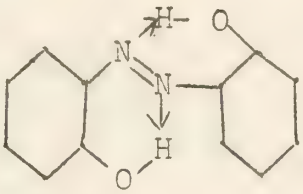
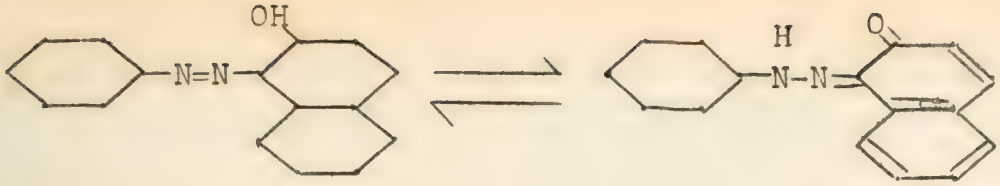


XV

Other interesting N→H bridges are the hydroxy azo dyes. Benzene azo-β-naphthol is insoluble in alkali in contrast to the p-hydroxy azo compound. In addition to the diazotization reaction it may also be prepared from β-naphthoquinone and phenylhydrazine. Due to resonance and chelation these compounds are identical thereby deciding another problem on chemical constitution.



Recently Zellhoefer, Copley, Marvel, et al., have studied extensively the formation of complexes through a particular type of hydrogen bonding O⟶H-C by determining solubilities in chloroform. Enough evidence has been accumulated to show that these bridges are real and important being related to a wide variety of experimental phenomena. In addition, this work permits one to generalize regarding the solubility of certain types of compounds.

Several chemical reactions have been used to distinguish compounds wherein hydrogen bonding occurs. For example, the o-substituted phenols in contrast with the m- and p-compounds give no compound formation with triphenyl chloromethane. In addition, it is also known that the methylation of a properly substituted ortho-phenol may be extremely difficult. This type of reaction has been extended to compounds such as naphthazarin, hydroxyanthraquinone, etc., which do not react with sarcosin anhydride, in contrast with their isomers.

The idea of hydrogen bonding is not only suited to explain definite physical and chemical properties but also applicable to stereochemistry and other problems of chemical structure.

It has been predicted that the most fruitful applications of the hydrogen bond theory will be to a better understanding of the nature and behavior of complicated organic substances such as gels, proteins, starch, cellulose, chlorophyl, hemoglobin, and related substances.

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Reported by L. A. Brooks
November 1, 1939

CIS-AZOBENZENE AND ITS SUBSTITUTION COMPOUNDS

G. S. Hartley -- Sir William Ramsay Laboratories, University College, London
A. H. Cook, D. G. Jones, and J. B. Polya -- Imperial College, London

The *cis*-isomer of azobenzene was first isolated by G. S. Hartley in 1937. He had observed that in attempts to estimate azobenzene by a colorimetric method the pure compound was decidedly darkened by exposure to light. He then found that by exposing an acetone solution to strong light and subsequently extracting with petroleum ether the *trans*-compound was largely removed. The *cis*-isomer could then be extracted with chloroform from which it crystallized as a red solid. This he showed to be the *cis*-isomer of azobenzene by the following evidence:

1. Melting point of the crystalline solid (determined by quick plunging) was 71.4° as compared with 68° of the normal variety. A plot of melting point against composition of mixtures of the two forms shows a drop to a eutectic at about 35°.

2. The dipole moment was measured and found to be 3.0 Debye units as compared to 0 for the ordinary form. Solubility of the new form was greater in polar solvents and less in nonpolar ones than the ordinary form.

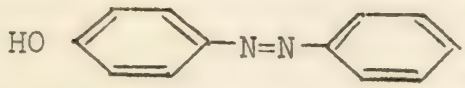
3. The preparative agent, light, is known to be active in promoting isomerization of *cis*- and *trans*-isomers. The new form is obtained from the normal form by action of light. It is completely changed to the normal form again when heated.

4. The change under the influence of heat from *cis* to *trans* could be carried out in a closed vessel without detectable change in the pressure of the gas above it. Therefore, the change was not associated with reaction with the air.

5. Molecular weight determined by freezing point depressions in benzene and acetic acid indicate that no polymer is formed.

Having established the existence of this isomer Hartley turned to a study of other such isomers and their relative stability. He studied a number of 4- and 4,4'-substituted compounds. With few exceptions these showed an increase in color intensity on exposure to light. In cases where it was possible to isolate the *cis*-isomer readily color standards were made up and a plot of color against composition from pure *trans* to pure *cis* was made. In cases where the isomer was too labile to be easily isolated it was assumed that the color change would be linear with composition. He measured the rates of isomerization under a variety of conditions. On examination of the data it became at once evident that the rate of non-

catalyzed isomerizations increased roughly with the increase of polarity and polarizability of the solvent. Only one exception was encountered: compound I isomerized abnormally fast in acetone. This exception he minimized on the ground that the compound was very sensitive to the presence of OH groups.



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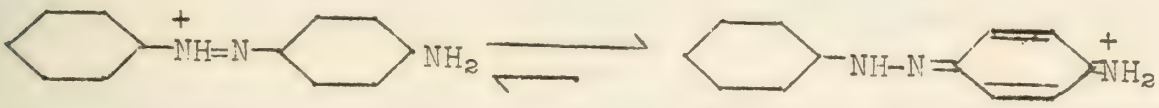
Further, that acetone theoretically always contains some enol and is relatively hard to keep anhydrous under experimental conditions. Hartley found that hydroxy, amino, and substituted amino compounds were very sensitive to acid and base catalysis, each being isomerized by that agent that would tend to convert it into the salt form. The following explanation was suggested:



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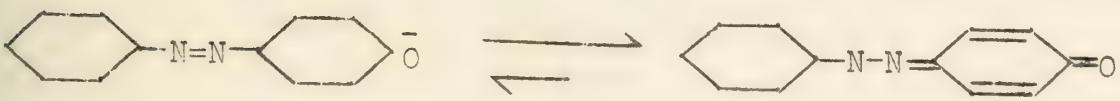
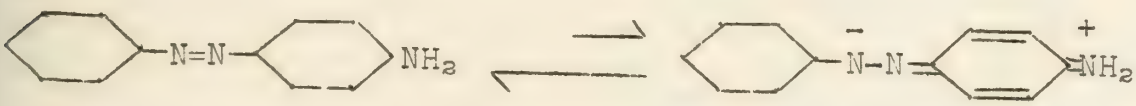
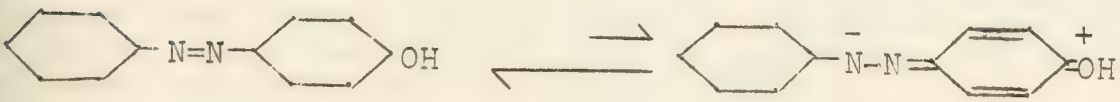


IV V

In the ionic form these compounds appear to exist as mesomers with properties best expressed by forms III and V.



VI VII



VIII IX

In nonionizing solvents the compounds exist primarily in the forms VI and VIII. Thus, in each case isomerization could take place through a form in which the nitrogen atoms are joined by a single bond. The speeds of isomerization are explained by the relative amount of material in the particular form.

Cook and coworkers put little faith in the mechanism above. They have extended the study to many compounds not treated by Hartley and have found many cases that are entirely unexplained by such a theory. Cook applied chromatographic analysis to the separation of the isomers with excellent success for those compounds of known stability. He showed that the order of stability of halogen substituted compounds with halogens in 4- and 4,4'-positions was I > Br > Cl. The cis-isomer of 2,2'-dimethylazobenzene was too unstable to be detected by color or chromatographic absorption. The cis-isomer of 3,3'-dimethyl- was detected. No benzene naphthyl azo or dinaphthyl azo compound was found that could be obtained in its cis-isomer. On the other hand a single substituent containing an element other than carbon and hydrogen almost always stabilized the cis-form enough to permit isolation.

Several cases were found in which a single substituent in one of the rings of azobenzene stabilized the cis-form enough to permit isolation whereas a second such group similarly placed in the other ring made the cis-form very unstable.

Three cases of polyazo compounds have been studied. Compound X was most completely described.

X

On preparing and purifying X it was found that the compound was chromatographically homogeneous. It was only slightly absorbed on activated Al_2O_3, and was readily washed out completely. However, after exposing for a short time to light and rechromatographing, two new bands of strongly absorbed material developed. The normal compound was washed out and the two bands separated. Of these only one yielded a crystalline product. This was the first and most firmly absorbed band; it gave a compound of melting point 136° (reverting on melting to the normal form of melting point 166°). On being kept in the dark for a short period and rechromatographed, this material gave only one band and an easily washed stain of the normal form. The second band gave an oily product which on standing overnight and rechromatographing gave two sharp zones just as did the original irradiated material. This is taken as clear evidence that the first zone was the trans-cis-isomer and the second the cis-cis-isomer.

Recently the data from absorption spectra of many of these compounds have been reported. The cis-compounds differ from the

trans- primarily in the intensity rather than the position of the maxima on the wave length scale. Two maxima are characteristically observed; one between 3200 and 3700 Å called K, another between 4400 and 4700 Å called R. K is attributed to the general conjugation between -N=N- and the two aromatic nuclei; R to the N=N linkage itself. It is found that the K maximum is shifted toward the longer wave lengths by substitution in the 4-position. K is by far the most intense absorptive region of the spectrum; this is true of both cis- and trans-isomers. K is regularly less intense in the cis form though the overall intensity of absorption of that form is greater.

A remarkable type of absorption spectrum was observed in the cases of 2,2'-methoxy-, ethoxy-, and hydroxyazobenzenes. These all possessed an intense maximum at 3800 to 4200 Å. No explanation of this effect was offered.

On stepwise isomerization of the cis-cis-compound (X) a regular decrease in intensity of absorption was observed. However, there was no regular shift of the position of the K band-head. The cis-trans-isomer gave a K maximum at shorter wave length than either of the other forms.

In summation of the reports thus far published it may be said that there is as yet no theory that can explain all the cases of stability or instability of cis-isomers. There has been considerable information published concerning isomers thought but not proven to be of the cis-trans-type. The rigid proof of the configuration must await dipole moment measurements. In most cases isomers have either been assumed to be cis if more highly colored; or have been assumed to be cis if different from the 'normal-trans' coupling product and convertible thereto by action of heat.

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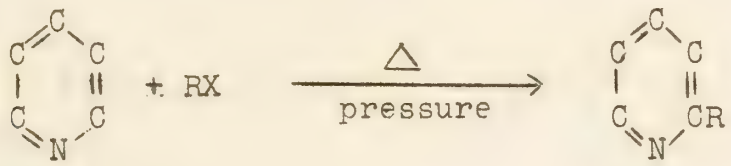
Reported by W. L. Walton
November 1, 1939

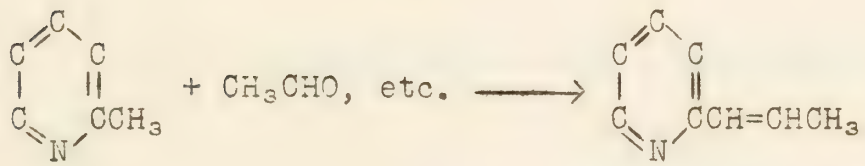
THE SYNTHESIS OF SUBSTITUTED PYRIDINES

A. E. Tschitschibabine -- Paris

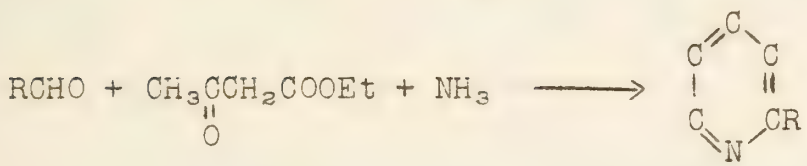
Pyridine and numerous of its homologs and derivatives are readily obtainable from coal tars and other sources. Certain ones, however, which are of especial interest in connection with the identification of alkaloids and other natural products are not thus available, and must be synthesized. Of the general methods that have been developed, the ones by Ladenberg (reactions I and II) and Hantzsch (reaction III) have been found useful, but are difficult, and the yields are low.



I



II



III

As early as 1860, Heubner and Geuther noted the formation of an oily substance resulting from the treatment of aldehyde ammonia with acrolein. Baeyer was the first to recognize the possibility of the synthesis of a substituted pyridine by this method, and he succeeded in identifying β-picoline as one product of the reaction. Isolated examples of similar reactions carried out by other investigators appeared from time to time, and early in the 1900's Tschitschibabine was struck with the possibilities of generalizing the reaction, using high temperatures and aluminum oxide as a catalyst to effect the condensation. A still better method of bringing about the condensation, namely, with ammonium acetate and pressure, was discovered much later, and through these two procedures, largely as a result of the researches of Tschitschibabine and his workers, the following generalizations have been established:

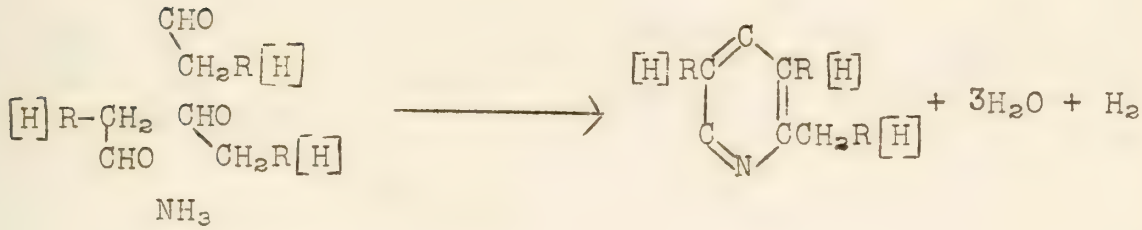
1. Reaction of unsaturated aldehydes and ammonia

According to Tschitschibabine, this proceeds in only one way.

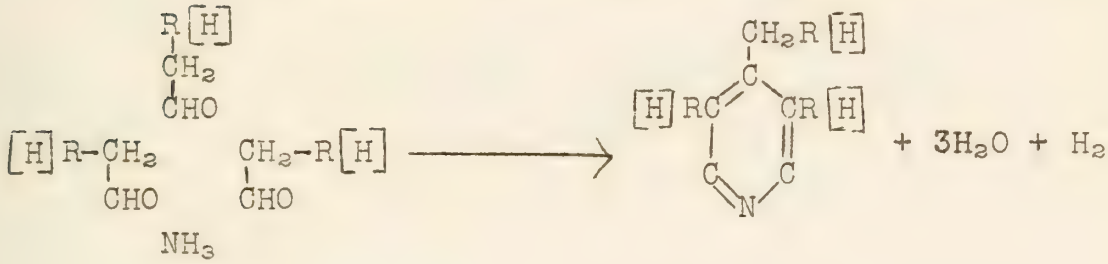
2. Reaction of saturated aldehydes and ammonia

(a) Acetaldehyde and its monosubstituted homologs

(1) α-Condensation at low temperatures (under 200°)

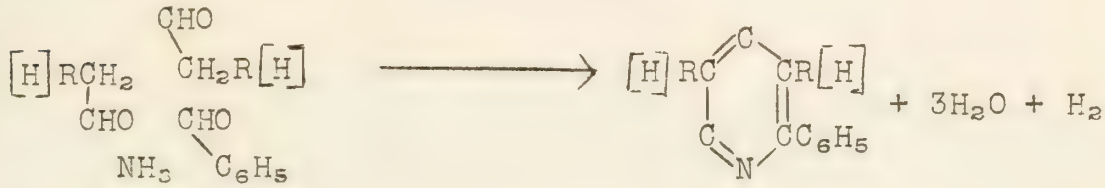


(2) γ-Condensation at high temperatures (300°)



(b) Mixtures of acetaldehyde and/or its monosubstituted homologs. Ten different substituted pyridines are theoretically possible.

(c) Mixtures of acetaldehyde and/or its monosubstituted homologs with secondary or tertiary aldehydes. Here the aldehyde that furnishes the sidechain may be secondary or tertiary. For example,

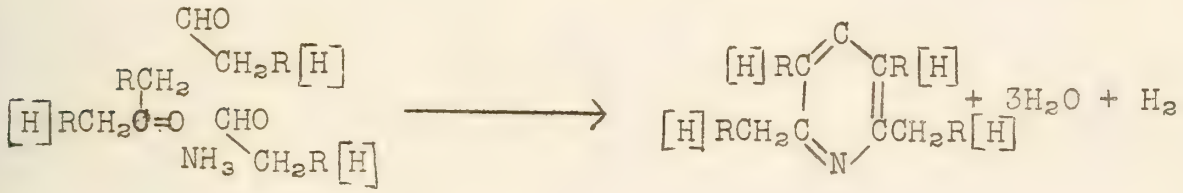


3. Reaction of ketones and aldehydes with ammonia

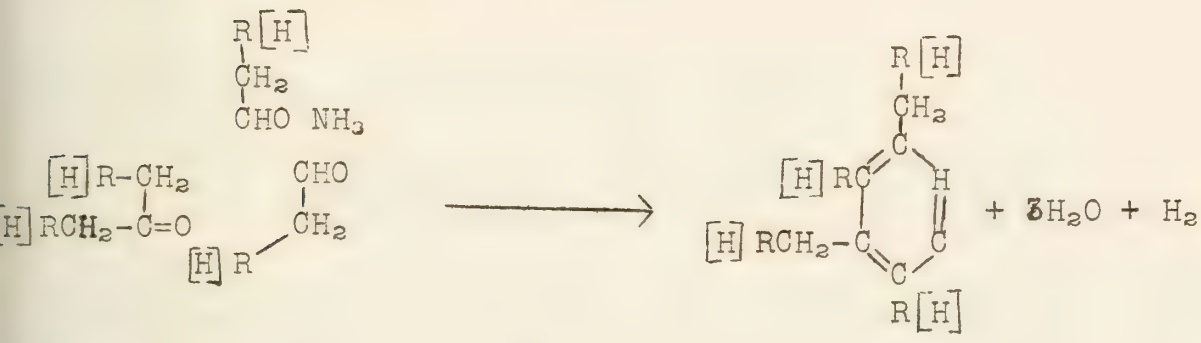
Ketones with the grouping $-CH_2\underset{\underset{O}{\|}}{C}-$ may replace either one or two aldehyde molecules.

(a) Condensations involving one molecule of aldehyde. When the aldehyde is other than primary, only two products are possible; with ketones of the type $RCH_2\underset{\underset{O}{\|}}{C}CH_2R'$, only four.

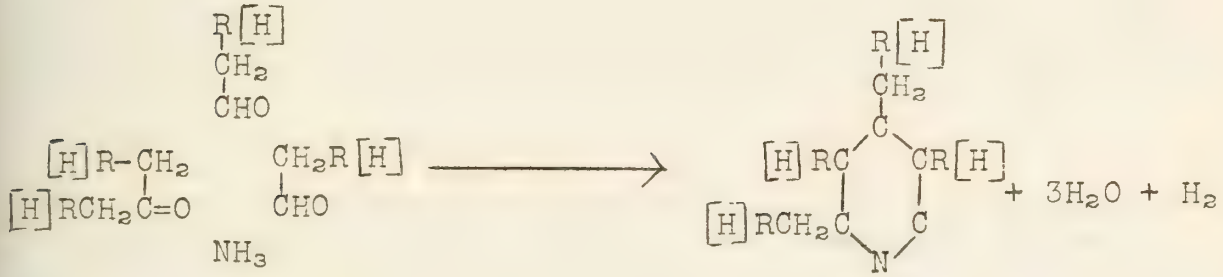
(b) Condensations involving two molecules of aldehyde. Here there are three possible ways in which the condensation may occur. These are designated α, α_1, and γ (reactions IV, V, and VI, respectively).



IV

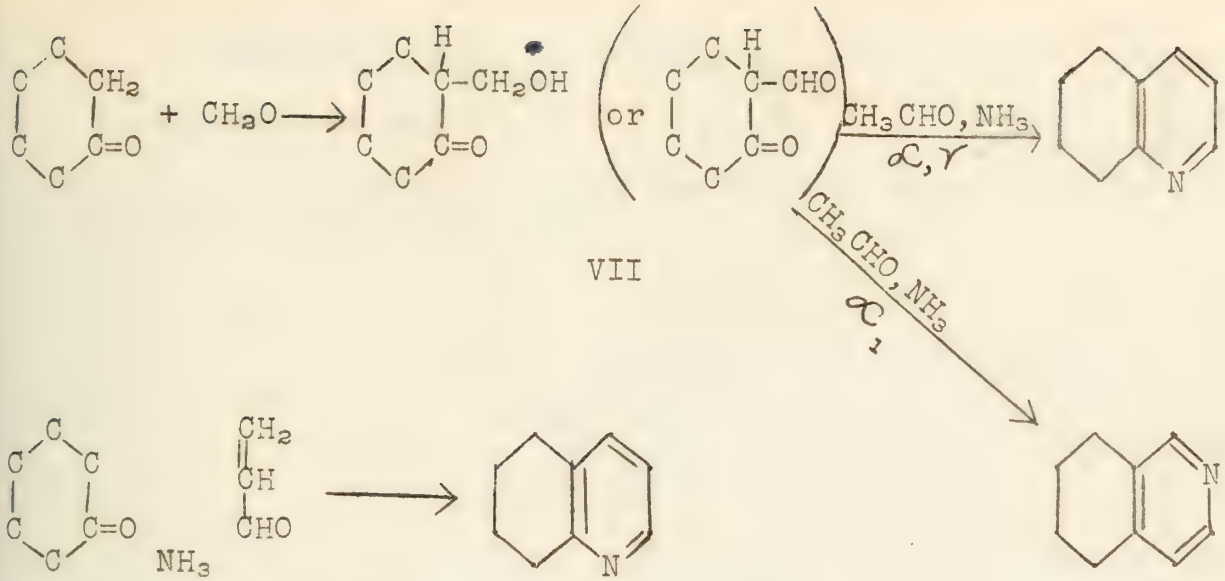


V



VI

These last reactions are interesting, since it might be expected that a mixture of cyclohexanone, acetaldehyde, and formaldehyde would produce tetrahydroquinoline through α- and γ-condensation, and tetrahydroisoquinoline through α_1-condensation. It is likely that these products would be more easily realized through a stepwise reaction (reaction VII), or through the use of acrolein (reaction VIII).



VII

VIII

The reactions reported in the latest paper are:

1. Cyclohexanone, formaldehyde, and ammonia
2. Cyclohexanone, acetaldehyde, and ammonia
3. Cyclopentadiene, acetaldehyde, and ammonia

In all cases the reactions were carried out in the presence of ammonium acetate in an autoclave at a temperature of about 180°. The neutral products of the reaction were separated by acidifying and extracting the solution with ether. The basic products were then obtained by basifying the solution. The material thus obtained, after evaporation of the ether used, was fractionated under reduced pressure, and the individual compounds purified and identified through the picrate salts.

Obtained from reaction 1:

(a) Thirty-four per cent of theoretical octahydrophenanthridine which, since it was previously unknown, was identified through oxidation to 2,3,4,5-tetracarboxy pyridine.

(b) Six per cent of theoretical octahydroacridine.

Obtained from reaction 2:

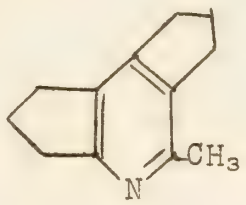
(a) Octahydromethylphenanthridine (in greatest amount)

(b) Octahydromethylacridine (totaling forty-seven per cent of theoretical)

(c) Some tetrahydroquinaldine

Obtained from reaction 3:

In rather smaller yield than above, a compound which probably has the structure



The reaction between formylcyclohexanone, acetaldehyde and ammonia is being investigated.

Bibliography:

Tschitschibabine et al., J. prakt. Chem., 107, 109, 122, 138 (1924); Bull. Soc. Chim., (5), 3, 762 (1936); (5) 4, 1826 (1937); (5), 6, 522 (1939)

Reported by L. O. Binder, Jr.
November 8, 1939

STUDIES IN THE TERPHENYL SERIES

H. France, I. M. Heilbron, and D. H. Hey --
The University, Manchester

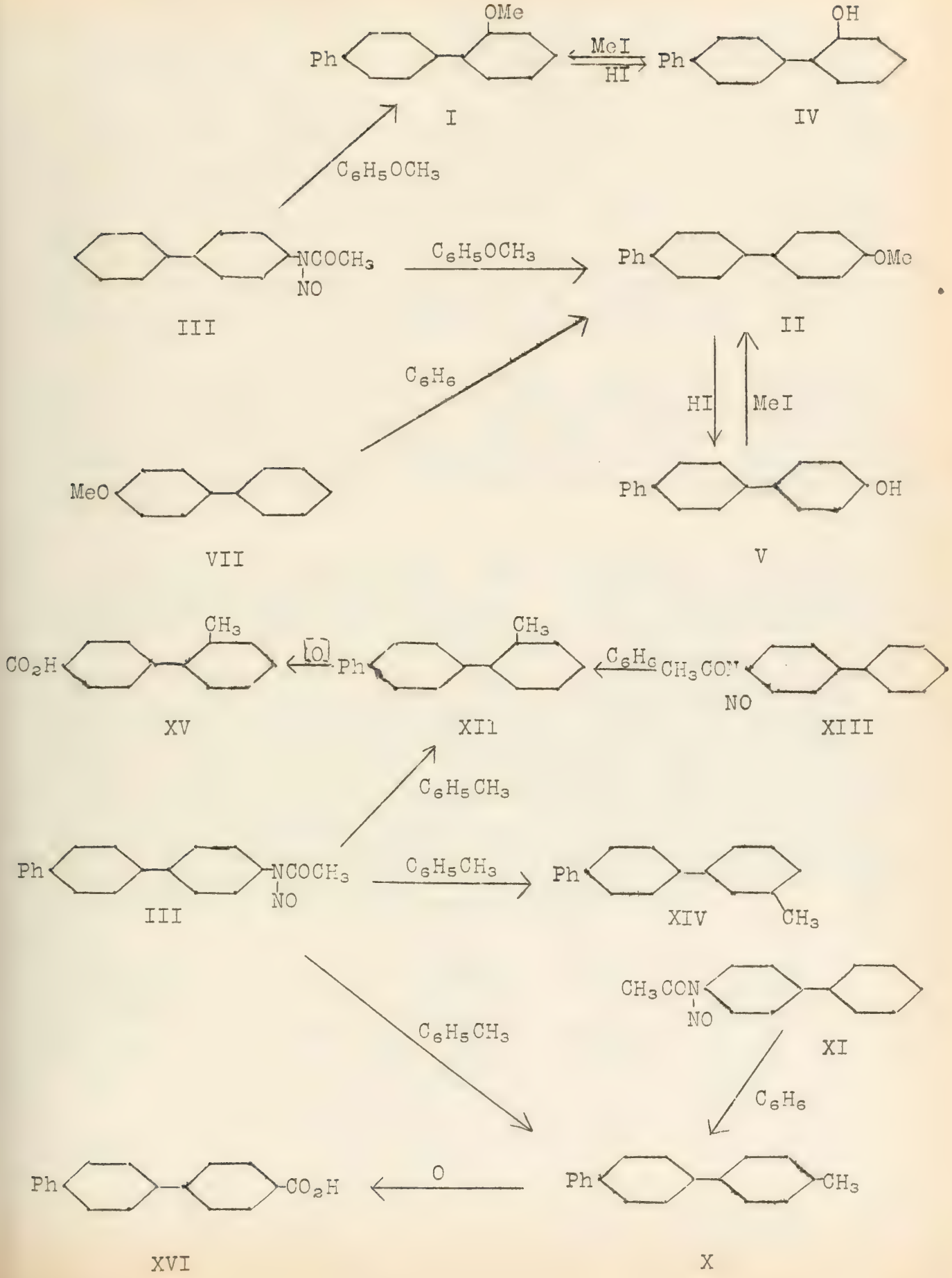
The only systematic investigations into the preparation of terphenyls have been made by the authors. Previously they investigated certain halogen, nitro, and amino derivatives. This study has now been extended to certain hydroxy and methyl derivatives of p-terphenyl and to the synthesis and nitration of m-terphenyl. They were able to prepare the terphenyl hydrocarbons in 50-60 per cent yields by the reaction, originally due to Bamberger in 1897, whereby a union of two aryl nuclei is affected by means of the reaction of an N-nitrosoacetylarylamine and an aromatic hydrocarbon thus:

$$ArN(NO)COCH_3 + A'rH \longrightarrow ArA'r + N_2 + CH_3CO_2H$$

Hydroxy Derivatives.--Monohydroxy derivatives have not been prepared heretofore, but 2-methoxy-p-terphenyl (I) and 4-methoxy-p-terphenyl (II) are now obtained by the interaction of 4-nitrosoacetamidodiphenyl (III) with anisole and on demethylation yield the corresponding hydroxy compounds (IV and V), the constitution of which have been determined. 2-Hydroxy-p-terphenyl (IV) is prepared by the decomposition of the diazonium sulfate of 2-amino-p-terphenyl (V) in hot aqueous solution, and on methylation yields 2-methoxy-p-terphenyl (I), identical with the product isolated in the reaction with anisole. The structure of 4-methoxy-p-terphenyl (II) is demonstrated by its identity with the compound synthesized by the interaction of 4'-nitrosoacetamido-4-methoxybiphenyl (VII) and benzene.

2,5-Dimethoxy-p-terphenyl (IX) was prepared by the reaction between III and liquid quinol dimethyl ether at 50-55°, and on demethylation yields the 2,5-dihydroxy compound (VIII), which is identical with the 2,5-dihydroxy-p-terphenyl previously described in the literature and prepared by condensation of diphenyl-4-diazonium chloride and benzoquinone followed by reduction of the resulting benzoquinone.

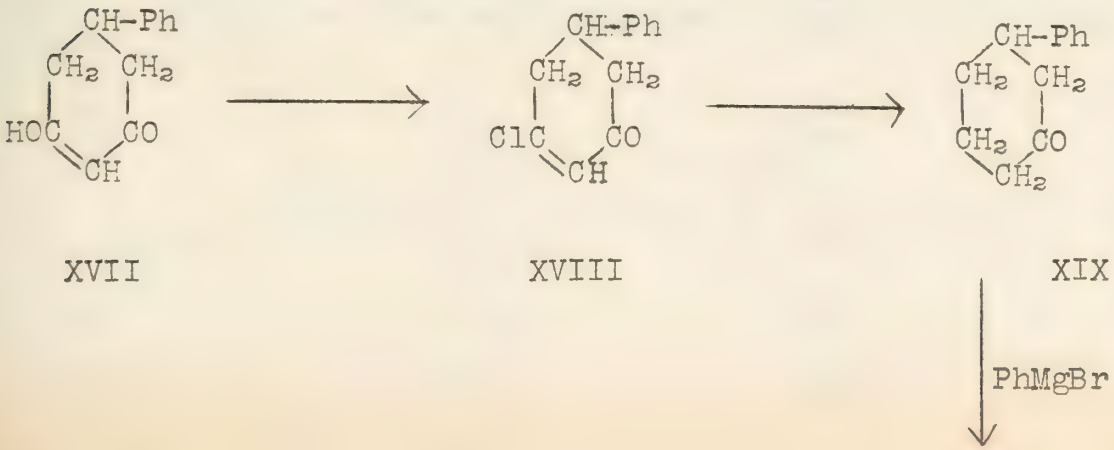
IX VIII VI

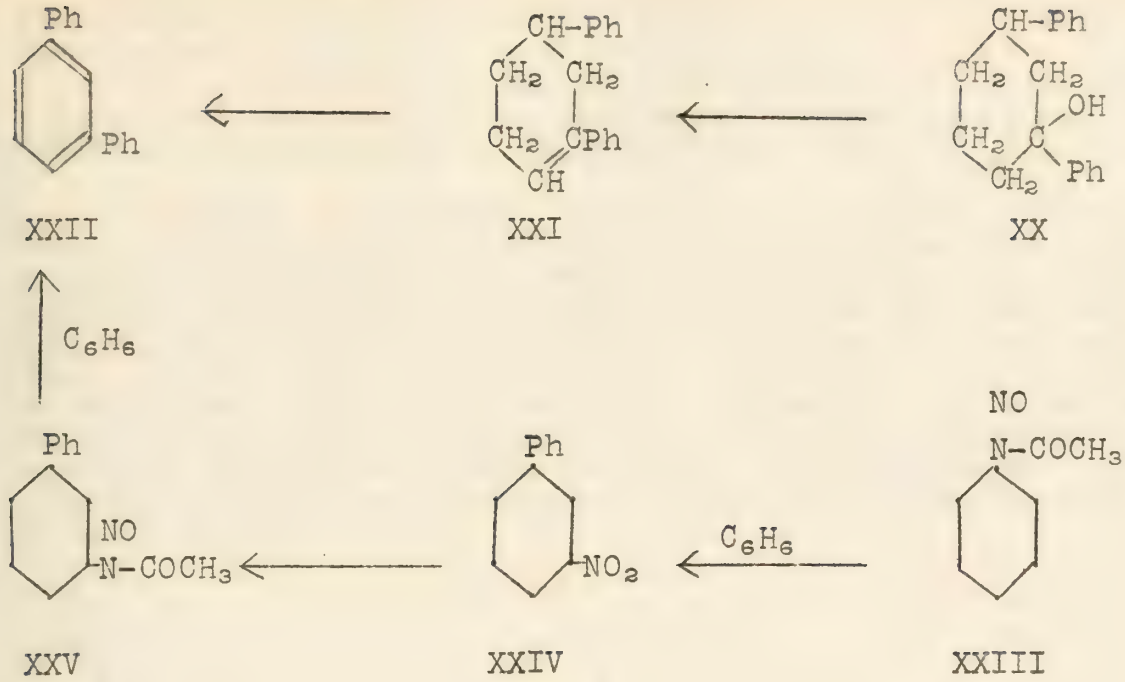

OMe
Ph
MeI
HI
OH
Ph
I
IV
$C_6H_5OCH_3$
NCOCH$_3$
NO
$C_6H_5OCH_3$
Ph
OMe
III
II
C_6H_6
HI
MeI
MeO
Ph
OH
VII
V
CH$_3$
CO$_2$H
[O]
Ph
CH$_3$
C_6H_6
CH$_3$CON
NO
XV
XII
XIII
$C_6H_5CH_3$
Ph
NCOCH$_3$
NO
$C_6H_5CH_3$
Ph
III
XIV
CH$_3$
CH$_3$CON
NO
XI
$C_6H_5CH_3$
C_6H_6
Ph
CO$_2$H
O
Ph
CH$_3$
XVI
X

Methyl Derivatives.--4-Methyl-p-terphenyl (X) was prepared by von Braun et al. from p-tolylmagnesium bromide and 4-cyclohexylcyclohexanone, followed by successive dehydration and dehydrogenation. Monomethyl derivatives are prepared by the authors by the reaction of 4-nitrosoacetamidodiphenyl (III) and toluene, in which a mixture of 3 isomerides is formed. After separation by fractional crystallization they had melting points of 207-208°, 169-170°, and 91-92°. The first corresponds with the 4-methyl-p-terphenyl (X) described by von Braun, and its identity further confirmed by synthesis from the reaction between the nitroso derivative (XI) and benzene. The third compound (m.p. 91-92°), is shown to be 2-methyl-p-terphenyl (XII) by its identity with the compound synthesized from the reaction between the nitroso derivative (XIII) and benzene. By elimination the compound of melting point 169-170°, present only in small quantities must be 3-methyl-p-terphenyl (XIV).

Oxidation of 2-methyl-p-terphenyl (XII) with chromic anhydride in acetic acid solution, gave, not the expected oxidation of the methyl group, but an acid which analysis showed to be a methyl biphenyl carboxylic acid (XV). On the other hand, oxidation of 4-methyl-p-terphenyl (X) in a similar manner gave p-terphenyl-4-carboxylic acid (XVI) identical with that previously described.

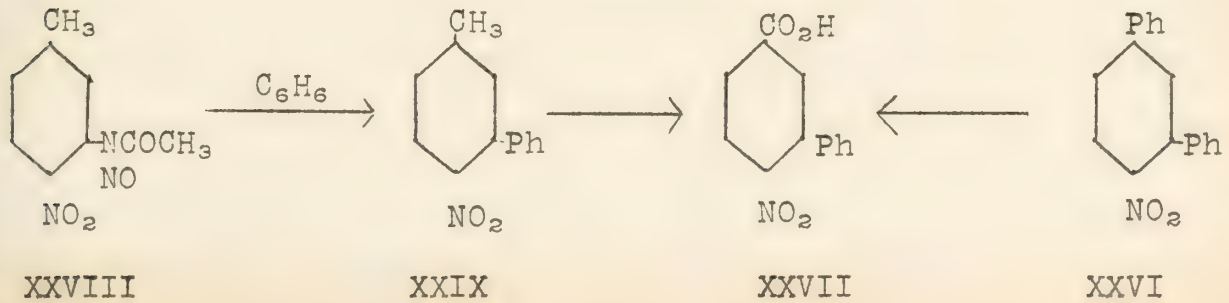
Synthesis of m-Terphenyl.--Two new methods of preparation of m-terphenyl have been developed. In the first, phenyldihydroresorcinol (XVII) readily prepared from benzilideneacetone and malonic ester, was converted by means of phosphorus trichloride in chloroform solution into 5-chloro-1-phenylcyclohexen-4,3-one (XVIII). This can be converted to phenylcyclohexanone (XIX) by reduction with sodium in moist ether to yield 3-phenylcyclohexanol, and oxidized to the ketone by oxidation with chromic acid. It is now shown that the chloroketone (II) can be converted directly into the ketone (XIX) by hydrogenation in the presence of a paladium catalyst. The ketone (XIX) was then treated with phenylmagnesium bromide to yield the tertiary alcohol (XX), was then dehydrated with formic acid to give 1,3-diphenylcyclohexene-3 (XXI) which then yields m-terphenyl (XXII) on dehydration with sulfur in boiling quinoline.





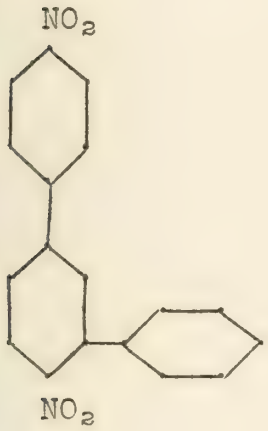
In the second method of synthesis, 3-nitrodiphenyl was prepared in 63 per cent yield from the reaction of nitroso-m-nitroacetanilide (XXIII) with benzene, was reduced to 3-aminodiphenyl, acetylate, and nitrosated to give XXV, which reacted with benzene to give m-terphenyl (XXII).

Nitration of m-Terphenyl.--The nitration of m-terphenyl previously by Wardner and Lowy led to the formation of several nitration products of unknown constitution. The nitration of m-terphenyl has now been reinvestigated. A mononitro derivative corresponding in properties to that described by Wardner and Lowy was obtained on treatment of m-terphenyl with concentrated nitric acid in glacial acetic at 85-90°. On oxidation it gave in good yield an acid, which was shown to be 2-nitrodiphenyl-5-carboxylic acid (XXVII), thus proving the mononitro derivative to be 4'-nitro-m-terphenyl (XXVI). The synthesis of the acid was affected by allowing the nitroso derivative (XXVIII) to react with benzene followed by oxidation of the resulting 2-nitro-5-methyldiphenyl (XXIX) to the required acid (XXVII).

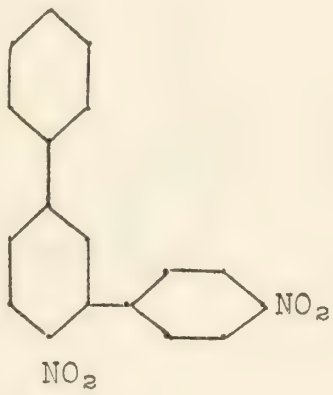


A dinitro derivative was prepared on treatment of the hydrocarbon with concentrated nitric acid at 90° for twenty minutes and on oxidation yielded p-nitrobenzoic acid. Nitration of either m-terphenyl or the 4'-nitro-m-terphenyl with fuming nitric acid gave a trinitro derivative unaffected by oxidation with chromic anhydride in glacial acetic acid.

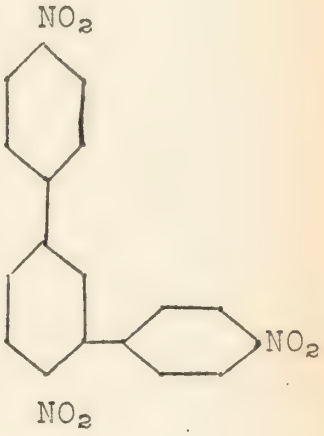
In regard to the constitution of the dinitro derivative, a nitro group in position 4' has been established and together with the fact that p-nitrobenzoic acid is obtained on oxidation suggests two possible structures, namely XXX and XXXI, but sufficient evidence is not available to make a choice between them. In the case of the trinitro derivative the resistance to oxidation suggests a nitro group in each of the three nuclei. One nitro group is at position 4' since further nitration of the mononitro derivative yields the trinitro-m-terphenyl. The remaining two nitro groups are most probably at positions 4 and 4" as in XXXII.



XXX



XXXI



XXXII

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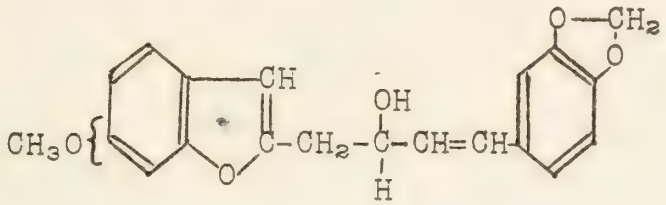
Wm. S. Grieve and D. H. Hey, J. Chem. Soc., 1797 (1934)
E. Bamberger, Ber., 30, 366 (1897)
C. A. Wardner and A. Lowy, J. Am. Chem. Soc., 54, 2510 (1932)
Wm. S. Grieve and D. H. Hey, J. Chem. Soc., 691 (1935)
von Braun, Irmisch and Nelles, Ber., 66, 1471 (1933)

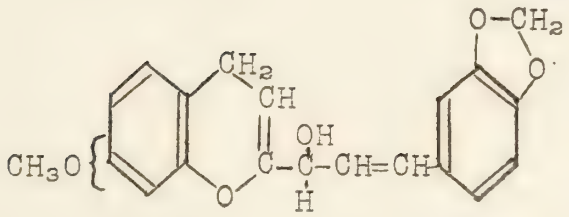
Reported by C. F. Huber
November 8, 1939

Kawai and associates -- Institute of Physical
and Chemical Research, Tokyo

Egonol was isolated by H. Okada from the nonsaponifiable portion of the seed oil of the Egonoki plant (Styrax japonicum, Sieb. et Zucc.). The colorless, silklike crystalline compound (m.p. 116°) was named egonol by M. Tsujimoto who discovered the presence of a hydroxyl and a methoxyl group in the molecule. The present investigators provisionally assigned structures I or I' on the basis of the following additional evidence:



I

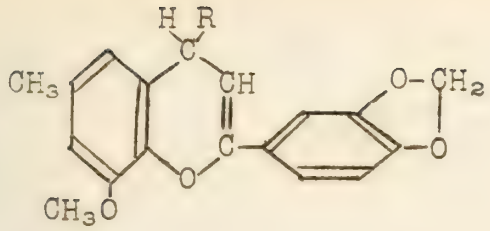


I'

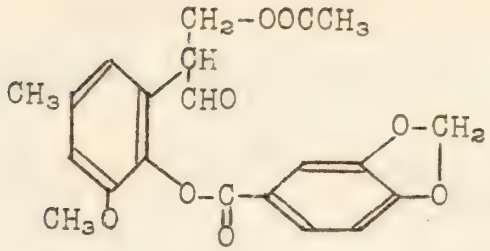
The empirical formula was found to be $C_{20}H_{18}O_5$. Permanganate oxidation gave piperonylic acid (VII). Failure to react with phthalic anhydride gave evidence of a secondary or tertiary hydroxyl group. The methoxyl group was assumed to be on a second aromatic nucleus, the presence of which helped for the low hydrogen-carbon ratio and the low reactivity with bromine. The remaining oxygen was placed in a phenolic ether linkage since mild alkaline fusion resulted in a phenolic derivative corresponding to the hydrolysis of such a linkage. Egonol was assumed present in the plant as an optically active fatty acid ester.

These structures were discarded when it was found that peroxide oxidation in acetic anhydride resulted in a new, water-soluble, ether-insoluble sirupy acid, the formulation of which could not be done readily on the basis of the above structures. Newer work set the empirical formula as $C_{19}H_{18}O_5$, and showed the hydroxyl group to be primary. Two new formulas (II and II') were proposed for the compound.

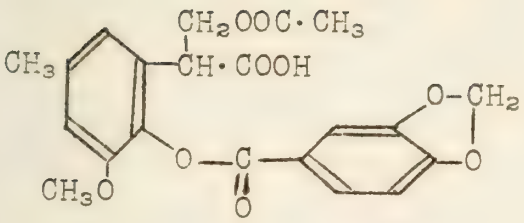
The results of the ozonolysis of acetyl egonol were explained on the basis of these.



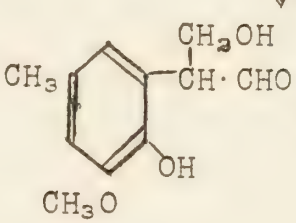
II R = OH
III R = CH_3COO-



IV

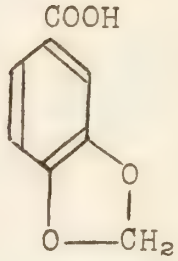


V

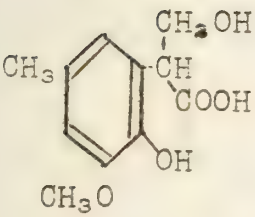


VIII

+

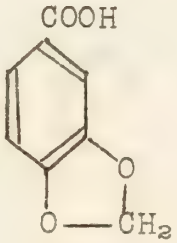


VII

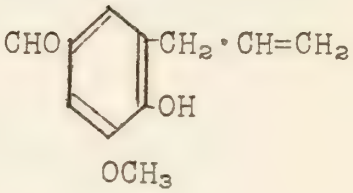


VI

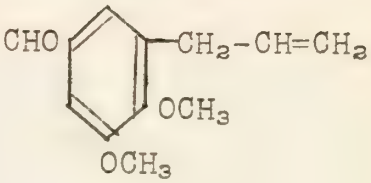
+

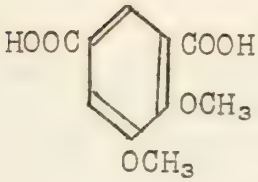


VII

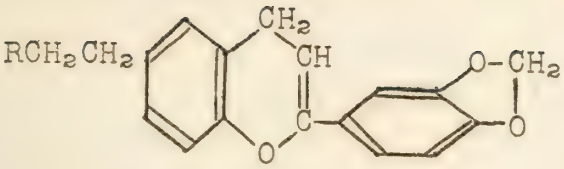


X

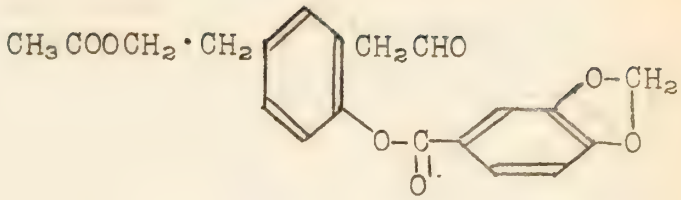




IX



II' R = OH
III' R = CH_3COO-

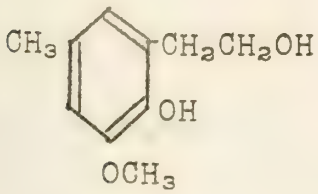


IV'

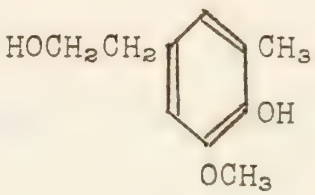
Ozonolysis of acetyl egonol (III or III') resulted in an aldehyde which was named acetyl styraxinic aldehyde (IV or IV'). Since this compound failed to give a Legal test (which compound IV' would be expected to give because of its $-CH_2CO-$ linkage), formula IV and its precursors were assumed more plausible. Acetyl styraxinic aldehyde (IV) oxidizes to acetyl styraxinic acid (V). Hydrolysis of IV gives piperonylic acid (VII) and the phenolic aldehyde (VIII) named styraxinolic aldehyde. The corresponding styraxinolic acid (VI) is obtained by hydrolyzing styraxinic acid. Methylation and oxidation of acid VI resulted in isohemepinic acid (IX), the structure of which was checked by synthesis.

Oxidation of acetyl egonol with perhydral resulted in styraxinolic acid along with a highly colored substance which was named noregonolonidine acetate, assumed to be a flavylium salt.

Heating styraxinolic acid <u>in vacuo</u> resulted in a product tentatively called decarbostyraxinolic acid (loss of a mole of CO_2). Structures XI or XI' would represent this compound if egonol is respectively II or II'. Both of these were synthesized but neither was identical with the naturally derived product.

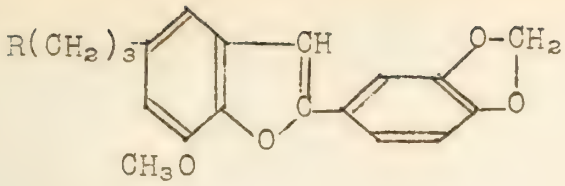


XI

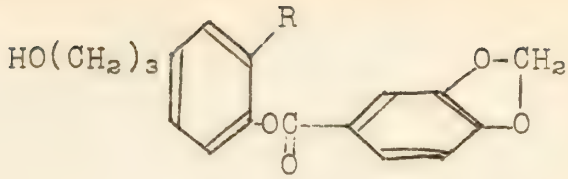


XI'

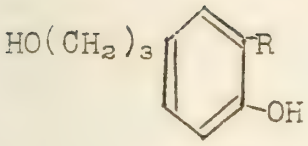
The investigators then returned to a coumarone formula (XII) for egonol. Decarbostyraxinolic acid would then be XVIII. Methylation and oxidation of the latter would be expected to yield veratric acid (XIX). This was found the case, establishing the structure of decarbostyraxinolic acid as that of dihydroconiferyl alcohol. The synthesis of the latter and of styraxinolic aldehyde establishes their structures as XVIII and XVI, respectively. The structure of egonol is represented by XII and of its derivatives as follows: acetyl egonol, XIII; styraxinic aldehyde, XIV; styraxinic acid, XV; styraxinolic aldehyde, XVI; and styraxinolic acid, XVII.



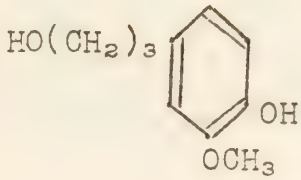
XII R = OH
XIII R = CH_3COO



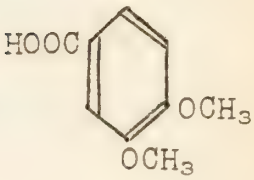
XIV R = CHO
XV R = COOH



XVI R = CHO
XVII R = COOH



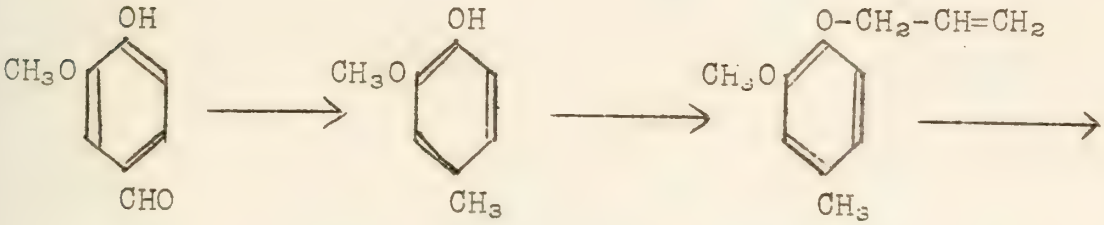
XVIII

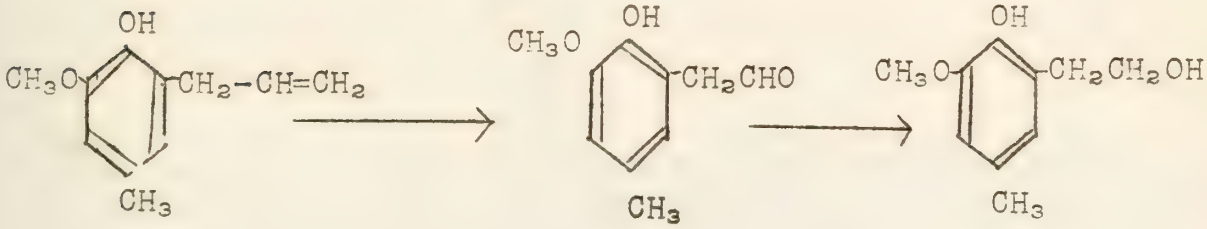


XIX

Mentioned syntheses were accomplished as follows:

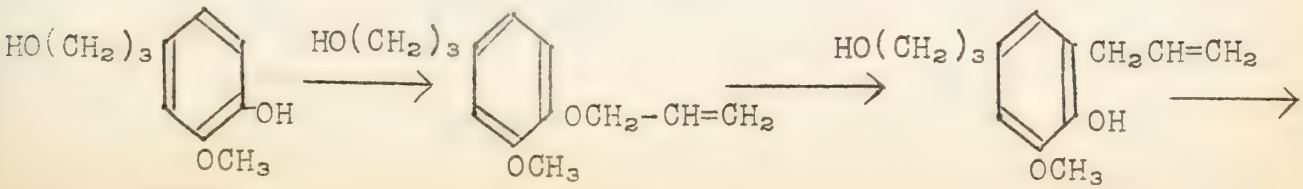
Compound XI:





XI

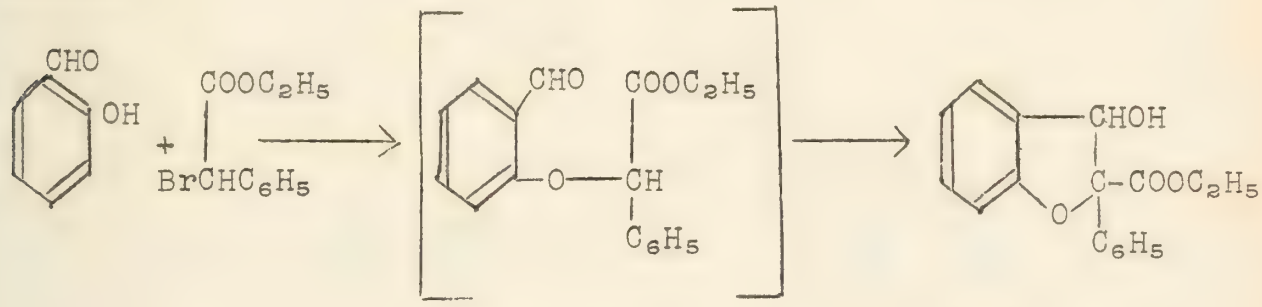
Compound XI' was obtained similarly from o-vanillin styraxinolic aldehyde (XVI):



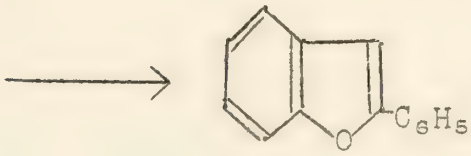
XVIII

XVI

Egonol was synthesized by a modification of Stoermer's synthesis of 2-phenylcoumarone (XXII) which involves reacting salicylaldehyde with α-bromophenylacetic acid. In an attempt to isolate intermediates in this synthesis, salicylaldehyde and ethyl α-bromophenylacetate were warmed with K_2CO_3 in methyl ethyl ketone, whereupon a coumarone derivative (XXI) was formed. This ester was hydrolyzed and heated in quinoline, giving 3-phenylcoumarone in better yields and more smoothly than the original method.

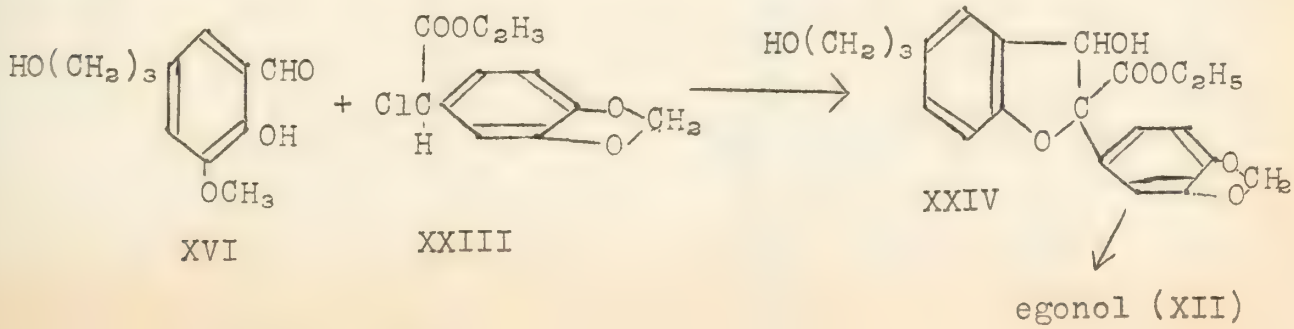


XX XXI



XXII

This constitutes a general preparation for 2-phenylcoumarones and derivatives. On substituting styraxinolic aldehyde (XVI) and α-chloro-(3,4-methylene dioxyphenyl)-acetic ester (XXIII) for the above reactants, egonol was prepared though in poor yields.

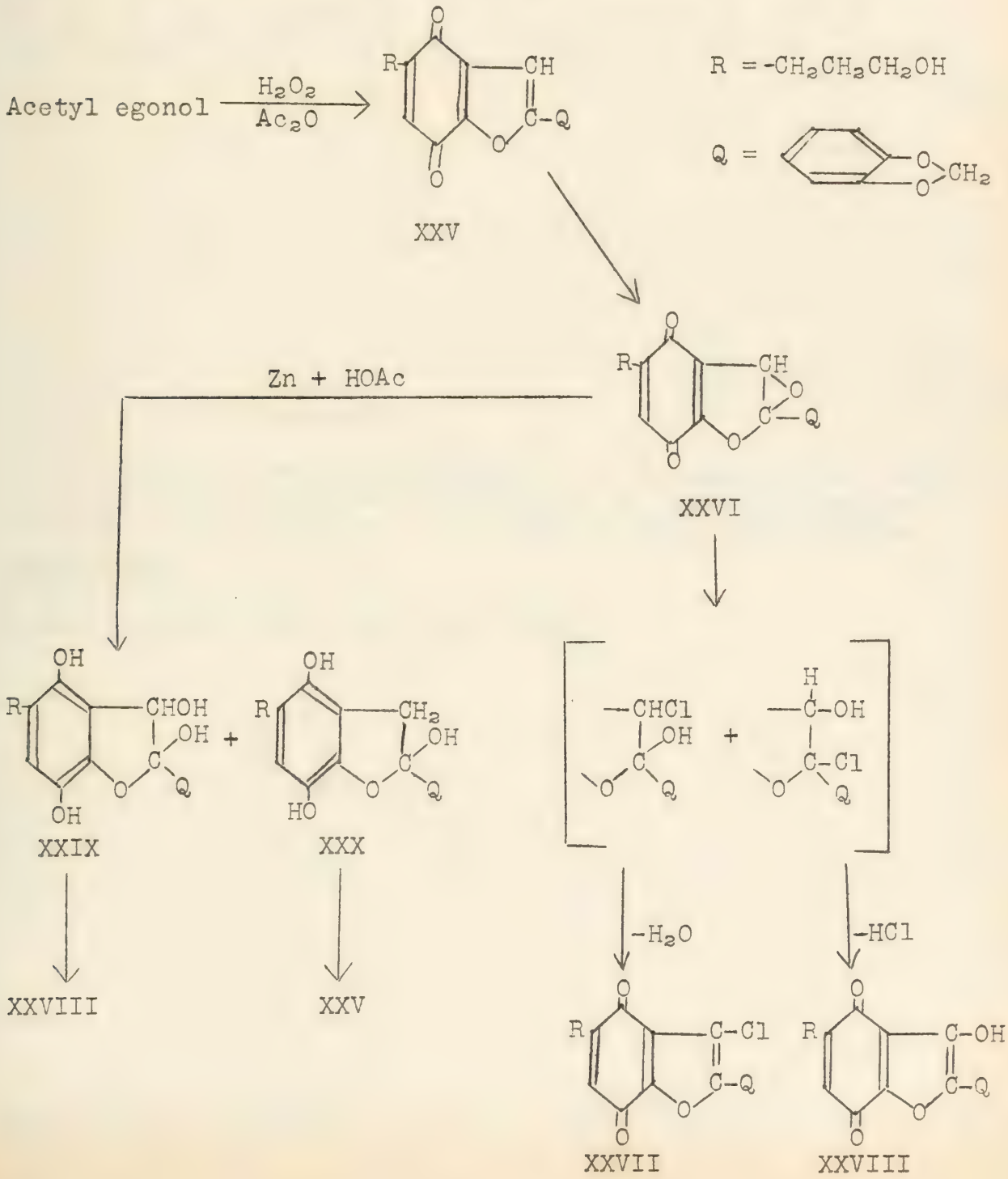


XVI XXIII

Earlier suspected optical activity of enzymatically hydrolyzed egonol from the fatty acid ester was found due to contamination by a phytosterol. The investigators failed to resolve egonol or styraxinolic acid.

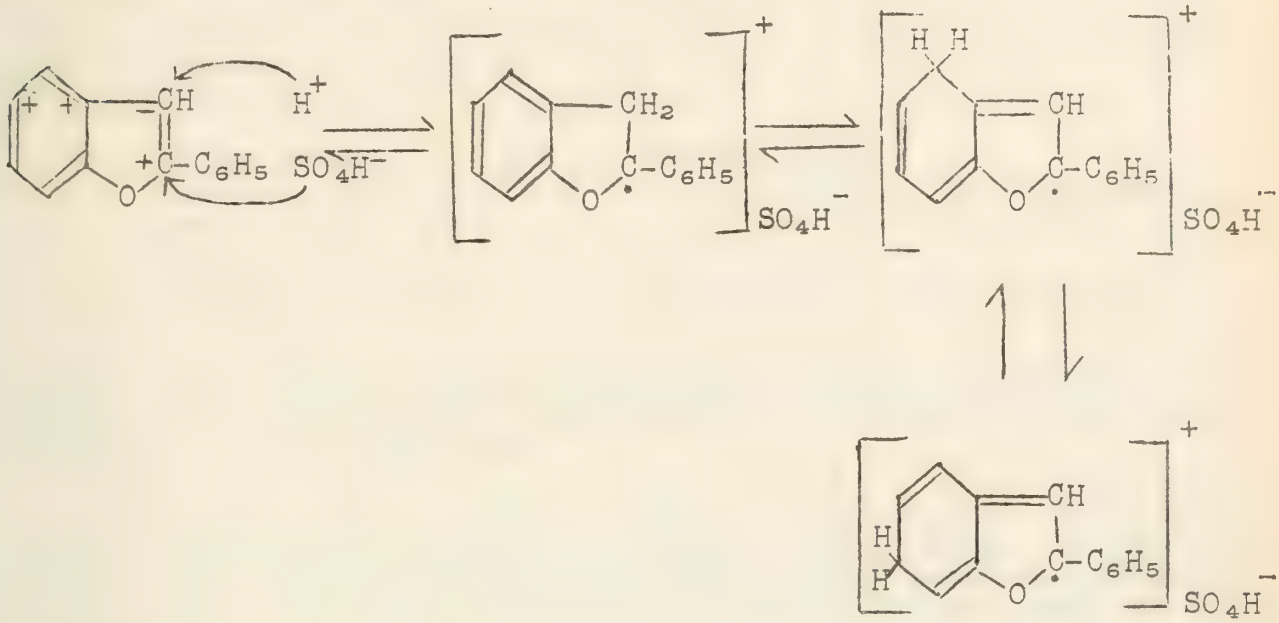
The formation of selenides and a Zerewitenoff analysis indicate the presence in egonol of an active hydrogen atom other than that of the hydroxyl group.

Among the peroxide oxidation products of acetyl egonol was found an intensely colored substance called noregonolonidine acetate. The following indicates a quinoid structure (XXV).



In these compounds the intensity of the color agrees with proposed structures. XXVI is yellow due to a quinoid structure. XXV, XXVII and XXVIII are deep violet due to unbroken conjugation throughout the molecule. XXX and XXIX are colorless.

The orange halochromic salt which egonol forms in sulfuric acid may be similar to that displayed by 2-phenylcoumarone which Stoermer explained as follows:



Although 2-phenylbenzopyrane is the skeleton of numerous plant products, egonol as a derivative of 2-phenylbenzofuran is the first representative of its class in the plant kingdom.

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Reported by J. W. Meier
November 15, 1939

EXCHANGE REACTIONS IN DEUTEROALCOHOL

Kharasch and Brown -- University of Chicago

Hydrogen exchange reactions consist in determining whether an exchange of light and heavy hydrogen atoms occurs when two compounds of different isotopic composition are brought together in solution at moderate temperatures. The chief method of determining hydrogen lability in organic compounds up until the work of Kharasch and Brown was by use of heavy water as the solvent and donor of deuterium. The following list shows a few of the results obtained:

formaldehyde	no exchange
malonic acid	all hydrogens exchange rapidly
acetic acid	exchange of carboxyl hydrogen only
sodium acetate	no exchange
methylamine hydrochloride	exchange of amino hydrogens

In all cases employing heavy water the exchange reactions are limited to those hydrogen atoms known to be labile on the basis of other types of reactions.

Kharasch and Brown made a series of experiments using heavy ethyl alcohol as the solvent and donor of deuterium. Besides the conventional type of hydrogen exchange, their results indicated a new type of hydrogen exchange involving hydrogen atoms in the benzene nucleus. Some of their results are given in the following table.

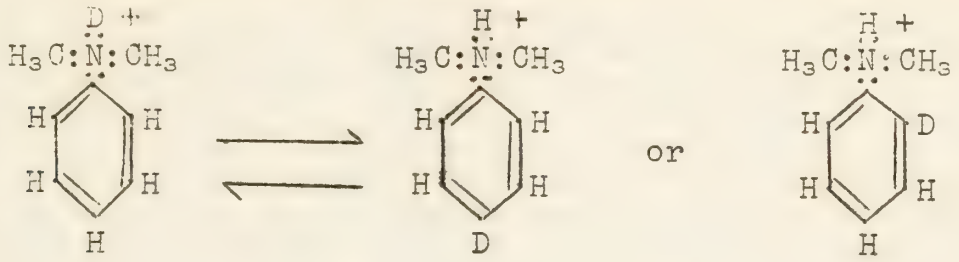
	Catalyst	Hydrogens Exchanged
Succinimide		1
Ethylacetoacetate		2
Dimethylaniline	--	0
	H_2SO_4	3
Fluorene	--	
	NaOH	2
9-Fluorenol	--	hydroxyl hydrogen
	NaOH	2
9-Methoxyfluorene	--	0
	NaOH	0
Diphenylmethane		0
Triphenylmethane		0
o-Nitrotoluene	--	>1
	NaOH	1
p-Nitrotoluene	--	0
	NaOH	1
Trinitrobenzene	--	0
	NaOH	3

Kharasch and Brown found that the hydrogen exchange in dimethyl aniline was catalyzed by sulfuric acid. Ingold, Raisin,

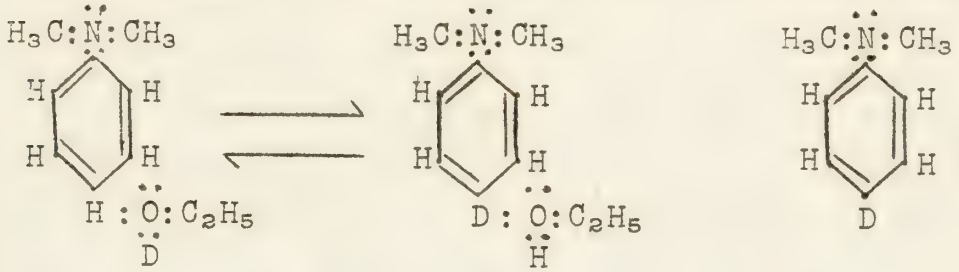
and Wilson had reported previously similar results with dimethylaniline using the hydrochloride in aqueous solution.

Three types of mechanisms were advanced to explain the results with dimethyl aniline:

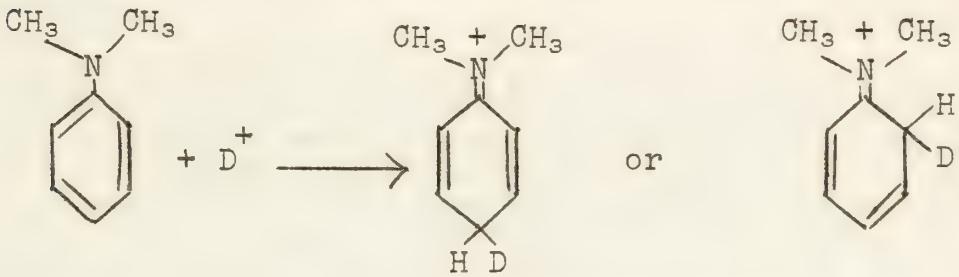
(1) Deuteron addition at the nitrogen atom followed by simple molecular rearrangement,



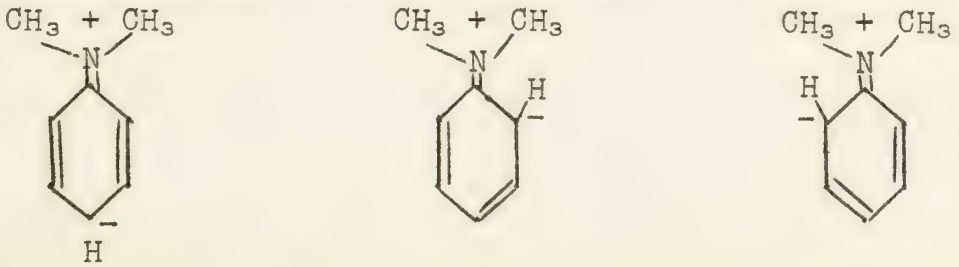
(2) Intermediate complex formation through a hydrogen bridge, followed by rearrangement and dissociation,



(3) Direct addition of protons at the nuclear positions giving rise to tautomeric forms of the salt,



This mechanism is suggested by the interpretation of the structure of the free base as a resonance hybrid of the normal resonance forms together with three zwitter ion forms shown below:



The free base is to be regarded, of course, as a single composite structure, but the effect of the pair of electrons normally available for salt formation on the nitrogen atom may be shared with two ortho positions and a para position makes more plausible the assumption that the molecule may accept protons at any one of these points. The products formed would no longer be resonance forms but tautomeric forms, and it will be evident that dissociation of the quinoid forms of the salt, but not of the normal form, will give rise to hydrogen exchange.

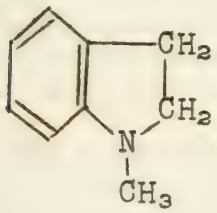
At first it was believed that the high electron density in the vicinity of the ortho and para carbon nuclei might lead to formation of hydrogen bridges, with the consequent labilization of the proton (mechanism 2). The fact that there was no exchange with diphenylmethane and triphenylmethane, weakly electronegative radicals, favors this mechanism. This theory was discarded in favor of mechanisms 1 or 3. If the normal ammonium salt acts an intermediate in the exchange reaction, any structural change decreasing the basicity of the molecule should also inhibit the exchange reaction. If, however, the structural change decreases the basic strength mainly by increasing the number or the stability of the zwitter ion resonance forms, and if the salts derived from these forms are intermediates, the exchange reaction should be facilitated. The experimental results are in accord with the hypothesis that quinoid forms of the salts act as intermediates. It was found that diphenylamine exchanges one hydrogen, presumably the nitrogen hydrogen, in the absence of acid, and seven in the presence of acid. Triphenylamine effects an exchange corresponding to nine hydrogens. This indicates that the ortho and para positions in each ring in addition to the hydrogen attached to the nitrogen are involved. Thus, despite the great decrease in base strength in the series dimethylaniline, diphenylamine and triphenylamine, the effect of substituting phenyl groups for methyl groups has been to increase the number of resonance structures and so to increase the number of points to which a proton may become attached.

Further evidence for the quinoid structure as intermediate in these reactions is given by the fact that substituents in the ortho position in dimethylaniline appear to inhibit the hydrogen exchange. Both the ortho-quinoid and para-quinoid forms of the aryldimethyl ammonium salts will possess a configuration such that the methyl groups are confined to the plane of the ring as a consequence, based on classical theory, of the presence of the nitrogen-carbon double bond. The effect of the ortho group, due to steric hindrance, consists in a tendency to prevent the alkyl groups from assuming this configuration, resulting in an increase of the energy of activation required for the formation of the reaction intermediate which is now a form of higher energy.

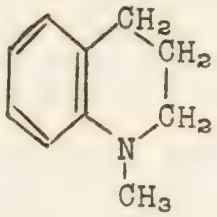
The proof of this theory of the ortho effect was carried out by two methods. One method used was to vary the size of the ortho substituent in the expectation that as the size of the group becomes smaller the inhibiting effect should diminish or eventually vanish. It was found that in ortho-bromodimethyl aniline and ortho-chlorodimethyl aniline there is a pronounced ortho effect in the failure to undergo hydrogen exchange under the conditions such that the exchange reactions of the corresponding meta and

para isomers are substantially complete. Ortho-fluorodimethyl aniline undergoes hydrogen exchange at an intermediate rate, showing that the effect is less conspicuous although not entirely absent.

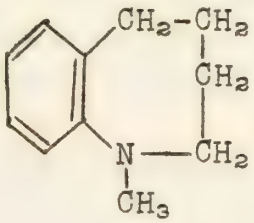
The second line of attack was based on the argument that if the amino nitrogen were to be linked to the carbon atom in such a way as to form a five-membered ring, as in N-methylindoline (I), which would necessarily be coplanar with the benzene ring, there



I



II

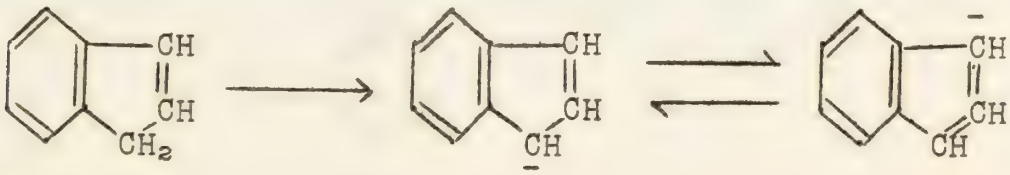


III

should be no ortho effect. A similar result was predicted for an analogous compound with a six-membered ring, N-methyl tetrahydroquinoline (II). With a highly puckered seven-membered ring, on the other hand, as in N-methyl homotetrahydroquinoline (III), the characteristic inhibition of the normal lability of the para and unsubstituted ortho hydrogen atoms should occur. It was observed that I and II exhibit a very high degree of reactivity in the exchange reactions, the former being more reactive but both exceeding dimethyl aniline; whereas III exchanges hydrogen at a relatively slow rate. These results provide rather convincing evidence that the key to the situation lies in the ability of the dialkylamino group to come into the plane of the benzene ring.

In the alkali catalyzed exchange reactions of the hydrocarbons containing a labile acidic hydrogen atom, there is evidence that a relationship exists between acid strength and rate of hydrogen exchange. Heuse has shown that indene and 9-phenylfluorene, both stronger acids than fluorene, exhibit hydrogen exchange under influence of alkali at least as readily as fluorene, whereas triphenylmethane and xanthane, intermediate in acidity, are also intermediate in their rate of hydrogen exchange.

The lability of hydrogen in indene and fluorene derivatives is explained if we assume as an intermediate a resonating anion formed by loss of a proton. This anion is electrically symmetrical about the beta-carbon atom and in the reformation of the



indene molecule by proton capture, the incoming proton could enter at either alpha position. The repetition of the processes of dissociation and recombination would then give rise ultimately to the exchange of three hydrogen atoms. Eberley has found that the exchange of indene corresponds to three hydrogen atoms. Among the derivatives of fluorene it has been found that in neutral solution only the hydroxyl hydrogen of 9-fluorenol will exchange, but in alkaline solution there is an additional exchange of the hydrogen atom in the 9-position as well. There is no exchange with 9-methoxyfluorene in alkaline or neutral solution. Thus, whereas the hydroxyl group appears to have no marked effect on the lability of the remaining hydrogen atom on the 9-position, a methoxy group has a very pronounced inhibiting effect.

The behavior of nitrotoluenes and 1,3,5-trinitrobenzene in deuteroalcohol is consistent with the interpretation that a low electron density around a carbon atom would facilitate the removal of a proton by hydroxyl ions. The nitro group markedly decreases the electronegativity of the phenyl radical. In acid solution trinitrobenzene would be a poor proton donor. In alkaline solution, however, with trinitrobenzene and ortho- and para-nitrotoluenes, substances which can exist in tautomeric forms, rapid exchange takes place.

In comparing the results of hydrogen exchange reactions in acetomesitylene and acetophenone, Kharasch and Brown concluded that the process of enolization in acetomesitylene is appreciably faster than in acetophenone. Kohler and Baltzly believed steric hindrance was the cause of the failure of acetomesitylene to exhibit the normal ketone reactions. Kharasch and Brown prefer to regard the lower reactivity of acetomesitylene in carbonyl addition reactions, as well as its greater tendency to enolization, as an effect due in part to the higher electronegativity of the mesityl radical as compared with the phenyl radical.

It will be obvious, in view of the parallel occurrence of ortho effects in hydrogen exchange reactions and in coupling, nitrosation, and condensation reactions of aromatic amines, that the elucidation of the nature of the effect for one type of reaction has important implications with regard to the others. There appears to be no obstacle in the way of extending the principles and the experimental approach of the present work to these related reactions.

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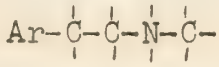
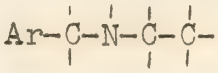
Reported by R. G. Handrick
November 15, 1939

ISOQUINOLINE AND ITS DERIVATIVES

Synthesis.--Isoquinoline and its derivatives have been synthesized by ring closure of compounds of type I or II.

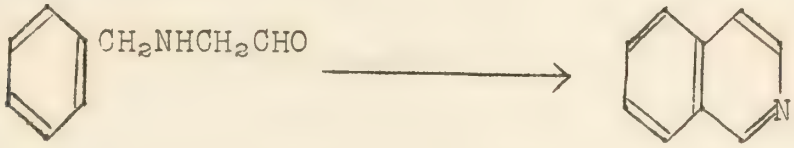


I



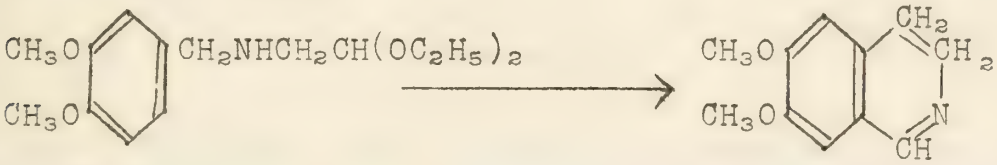
II

Ring closure of compounds of type II is usually rather difficult. However, Emil Fischer in 1893 obtained isoquinoline by treating benzylaminoacetaldehyde (III) with fuming sulfuric acid.



III

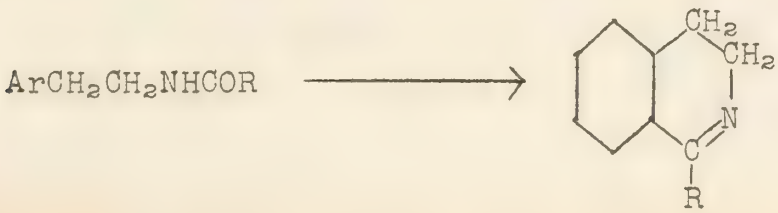
Rügheimer and Schön (1909) prepared 6,7-dimethoxy-1,2-dihydroisoquinoline by treating the acetal (IV) with sulfuric and arsenic acids.



IV

More recently Dey and Govindachari found that ring closure readily took place with substituted phenyl ethyl amines but not with benzyl amines.

The formation of isoquinoline derivatives from the β-aryl ethyl amines is accomplished by (1) forming the amides (V) with acyl or aroyl halides and then dehydrating with reagents such as phosphorous pentoxide or phosphorous oxychloride, and by (2) condensing the amines with aldehydes in the presence of reagents such as phosphorous pentachloride, phosphorous oxychloride, hydrochloric acid, etc.



V VI

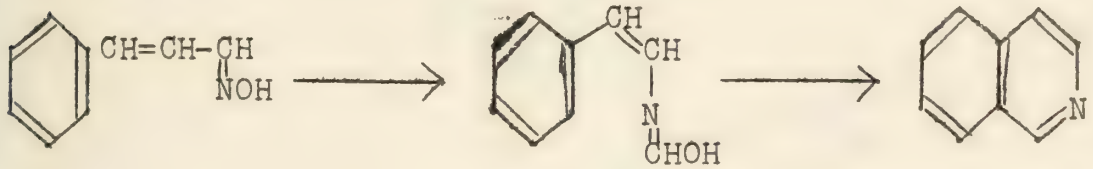
The second method was described first by Decker and Becker in 1913. The use of formaldehyde itself usually results in low yields. However, fairly good yields are obtained if activating groups such as methoxy or hydroxy are placed meta to the side-chain in the original β-aryl ethyl amine.

The dihydroisoquinoline derivatives (VI) may be dehydrogenated easily in good yields by means of palladium sponge to the corresponding isoquinoline derivatives. The method used particularly by Pictet and Krabbe, eliminates this dehydrogenation step. By starting with compounds of the type shown in formula VII a ring closure, if effected by use of phosphorous pentoxide, will at the same time lose a second mole of water and give the desired isoquinoline derivative directly.

$ArCHOHCH_2NHCOR$

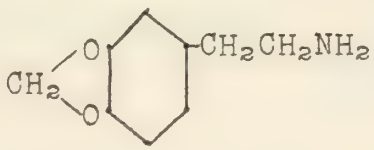
VII

An interesting synthesis of isoquinoline was effected by Bamberger and Goldschmidt. They found that both stereoisomers of cinnamicaldoxime on distillation with phosphorous pentoxide undergo the Beckmann change and give isoquinoline.

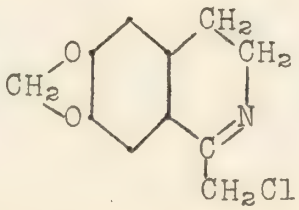


Child and Pyman first prepared 1-halogen alkyl derivatives of dihydroisoquinoline by treating β-aryl ethyl amines with properly substituted aryl halides. Ring closure was then effected by use of phosphorous oxychloride. They worked with the dimethoxy compounds, being interested in the physiological properties of some of these derivatives. They were unable, however, to prepare the 1-chloroethyldihydroisoquinoline because hydrogen chloride split out forming vinyl compounds.

Dey and Govindachari have extended this method by using the halogen substituted acid anhydrides. For example, by treating homopiperonylamine (VIII), with chloroacetic anhydride and subsequently with phosphorous oxychloride they obtained 1-chloromethyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (IX).

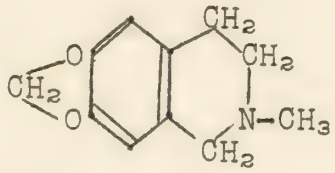


VIII



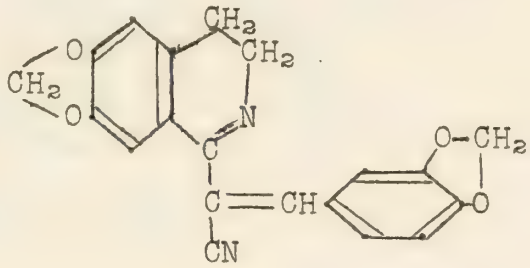
IX

Importance of Isoquinoline Derivatives.--The compounds of the type shown in formula IX are of interest because of the possibility of preparing physiologically important derivatives from them due to the extreme reactivity of the halogen atom. The chloride atom in IX may be readily replaced by hydroxyl and cyanide groups by treatment with potassium hydroxide and potassium cyanide, respectively. When compound IX is reduced by zinc and sulfuric acid the N-methyl trihydroisoquinoline derivative is formed.



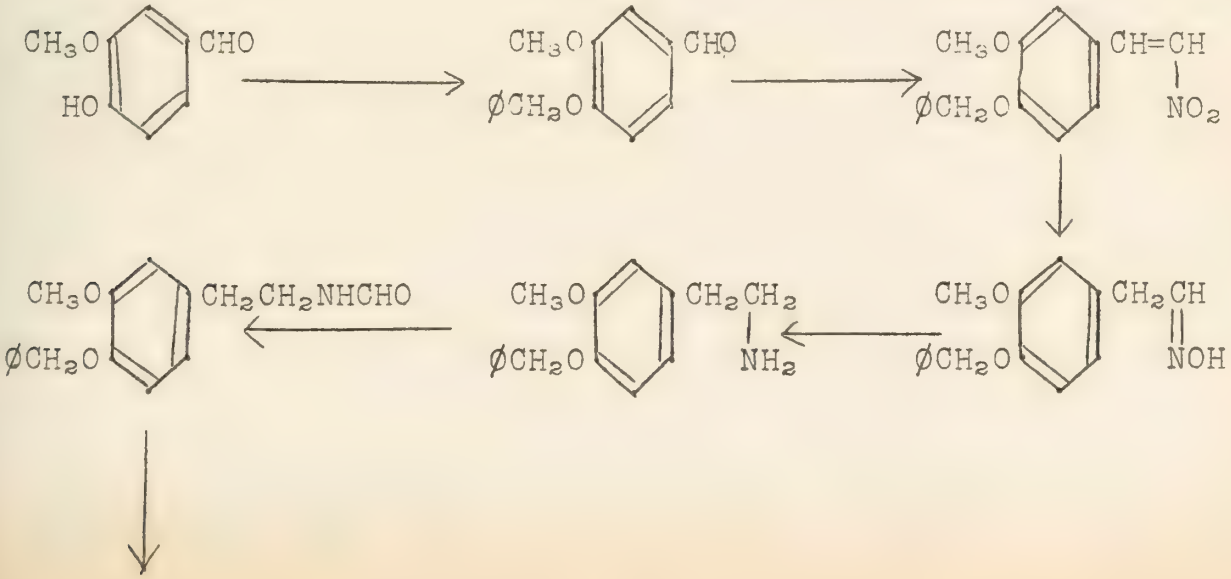
X

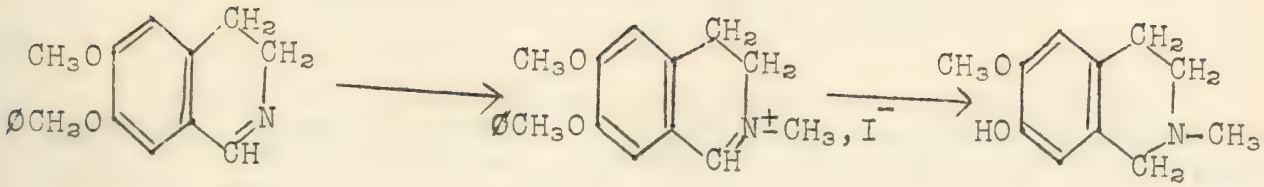
If the chloride atom is IX in replaced by cyanide the methylene group between the cyanide and carbon-nitrogen double bond becomes very reactive. It will condense with aldehydes to give, for example, with piperonal compound (XI).



XI

Recently Manske has synthesized the alkaloid corypalline (XII), by making use of the phosphorous pentoxide ring closure.





XII

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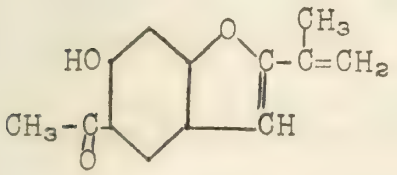
Reported by T. W. Mastin
November 22, 1939

BENZOFURAN DERIVATIVES

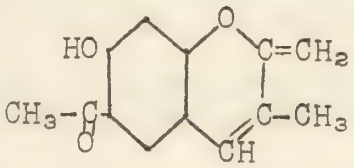
STRUCTURE OF EUPARIN

Robertson -- University of Liverpool

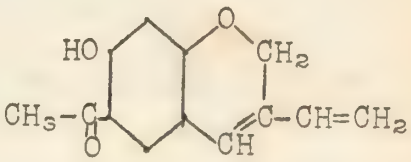
Euparin can be isolated from the roots of Eupatorium purpureum (purple boneset). It was first isolated by Lloyd about 1870, but very little was known of its structure until the work of Robertson and Kamthong. By analysis of euparin and its derivatives they assigned the formula $C_{13}H_{12}O_3$. The structure was limited to three possibilities (I, II, and III) by the following data:



I



II



III

1. Euparin is sparingly soluble in dilute aqueous sodium hydroxide; it forms monocarbonyl derivatives (2,4-dinitrophenylhydrazone, oxime, and semicarbazone), a monoacetate, and a mono-o-methyl ether; it gives a green color with ferric chloride in ethanol.

These data indicate a phenolic hydroxyl ortho to a carbonyl group in the molecule.

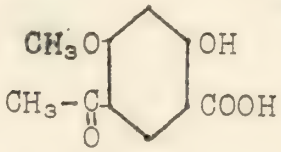
2. It is reduced catalytically to a tetrahydro derivative (which gives a red ferric chloride reaction in ethanol and forms an o-methyl ether, an oxime, and a 2,4-dinitrophenylhydrazone). Euparin forms an addition product with maleic anhydride.

These facts indicate that there are two double bonds which form a conjugated system and that the carbonyl is a ketone.

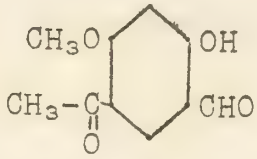
3. The amide obtained by a Beckmann rearrangement of the oxime of reduced euparin is regenerated from the amine by acetylation.

$$\text{oxime} \xrightarrow{SOCl_2} \text{amide} \underset{KOH}{\overset{Ac_2O}{\rightleftharpoons}} \text{amine}$$

Hence, the carbonyl is present as a methyl ketone.

4.  (IV) is obtained by oxidation of the methyl ether. This degradation product establishes the relative positions of substituents and shows that the third oxygen is an ether linkage of the aromatic ring with a C_5 residue having two double bonds.

5. Ozonolysis of o-methyl euparin gives formaldehyde and



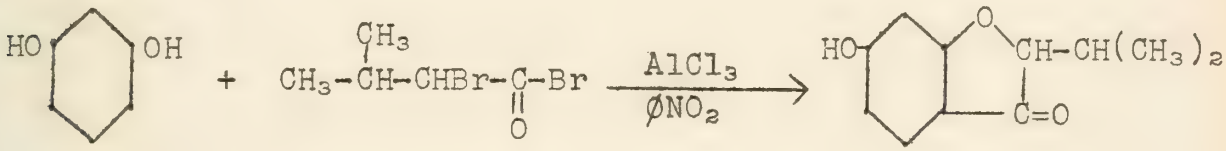
V

The formation of this product indicates that euparin contains a double bond once removed from the benzene ring and a vinyl group in the C_4 residue. These form the conjugated system.

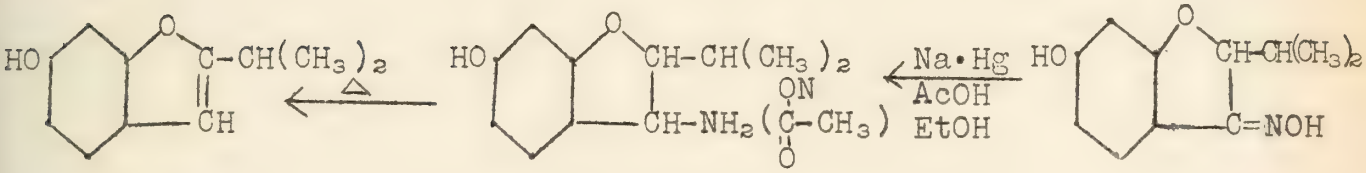
6. A small amount of isovaleric acid was produced in an attempt to deacetylate tetrahydroeuparin.

This suggests that tetrahydroeuparin is an isopropyl-coumaran such as would be obtained by reducing I.

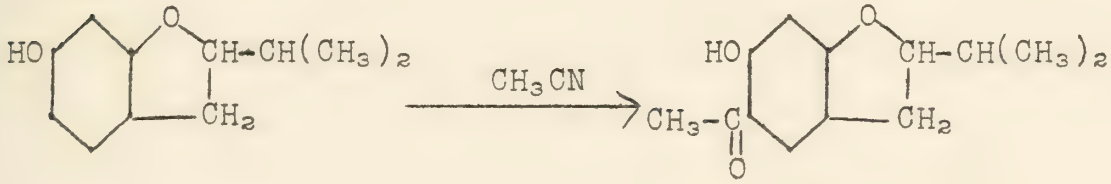
Tetrahydroeuparin corresponding to I was synthesized as follows:



VI



IX VIII VII



X XI

The compound XI so prepared was identical with the tetrahydro derivative obtained from euparin. The structure of euparin itself, therefore, is represented by I.

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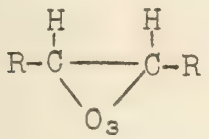
Reported by Alice Billman
November 22, 1939

OZONATION AND THE STRUCTURE OF OZONIDES

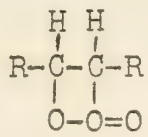
E. Briner et al. -- University of Geneva

The classical work of Harries and his coworkers has led to some remarkable contributions in the field of ozonation. In general, Harries was primarily interested in the products of reductive scission and their yield. He did little work toward the determination of the actual products which could be isolated under normal or nonreducing conditions.

Various investigators since Harries have suggested possible structures for ozonides. Three of the proposed structures are given below.



I



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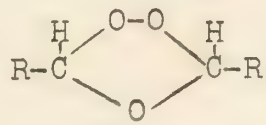


III

The objections to the noncommittal formula (I) used by Harries are obvious, while that proposed by Erdmann (II) is subject to almost the same objections as I, namely, reduction should give glycols. It is not considered likely that a C-C bond remains in ozonides. Formula III proposed by Staudinger is backed by a great deal of experimental evidence. Since Harries had found that ozone was reemitted from the ozonide of fumaric acid, Staudinger and Rieche proposed the preliminary formation of II, the so-called molozonide form which subsequently rearranges irreversibly into III.

Briner and his coworkers are attempting to determine the exact mechanism of the oxidation by ozone. They have followed the course of nonreductive scission of ozonides to give an aldehyde or ketone and an acid.

$$R\text{-}CHO_3HC\text{-}R' \longrightarrow \begin{cases} R\text{-}CHO + R'COOH & \text{(a)} \\ R'\text{-}CHO + RCOOH & \text{(b)} \end{cases}$$

As far as energy considerations are concerned there is no choice between a or b, since the following is true for most aldehydes.

$$R\text{-}CHO + [O] \longrightarrow R\text{-}COOH \qquad \Delta H = -70 \pm 1 \text{ cal.}$$

The authors have found that water is <u>not</u> necessary for the scission reaction but that it accelerates the reaction by either a or b. Water also causes extensive disintegration of the ozonide molecule as evidenced by the large amount of CH_2O and CO_2 given off.

Equations for the scission of ozonides are frequently balanced by assuming the evolution of oxygen or the production of HOOH which can subsequently oxidize part of the aldehyde present. Harries' contention that O_3 is evolved from the ozonide of fumaric acid has been referred to previously.

$$CH_3OOC\text{-}CH{=}HC\text{-}COOCH_3 + 2\ O_3 \longrightarrow 2\ OHC\text{-}COOCH_3 + 2\ O_2 \qquad \text{Eq. I}$$

methyl fumarate

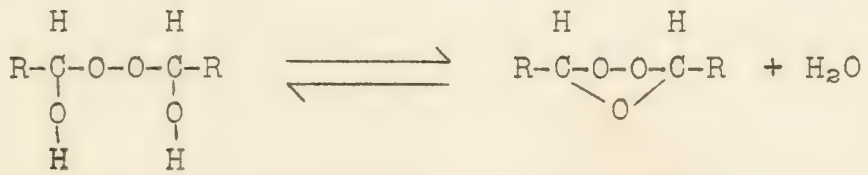
$$CH_3\text{-}CH{=}HC\text{-}COOH + O_3 + H_2O \longrightarrow CH_3\text{-}CHO + OHC\text{-}COOH + H_2O_2 \quad \text{Eq. II}$$

In regard to Equation I, the authors have never found more than a trace of oxygen in the gaseous products of ozonolysis. In regard to Equation II, hydrogen peroxide is never found in amounts which even approach that called for in the equation. A consideration of the energetics of the reaction as given in Equation II does not favor this type of reaction. The highly exothermic reaction of scission ($\Delta H = -56$ cal.) favors the reaction as written in a or b.

Investigation of the heats of ozonation indicates that the ΔH for the reaction is from -80 to -120 cal. for various ozonides. This would indicate that ozone is strongly bound in the ozonide molecule and would scarcely be eliminated as such, nor would we expect oxygen to be given off. Investigation of the ozonation of fumaric acid showed that ozone is not given off from this ozonide. The postulation of the preliminary molozonide form is no longer tenable, or necessary.

Briner has shown that ozonides exhibit peroxidic properties such that they can be titrated with potassium iodide. The ozonide will also react by reductive scission with three molecules of bisulfite to give two molecules of the aldehyde bisulfite derivative and one of bisulfate. Firm binding of the ozone in the ozonide does not contradict peroxidic properties since, for example, it is known that peroxides exhibit peroxidic action without giving off any oxygen as such.

In reference to Staudinger's formula (III) we note that one of the oxygen atoms functions as an anhydride oxygen. Peroxidic property must, therefore, be a function of one or both of the other oxygen atoms. The ozonides are linked with the peroxides on one hand and the anhydrides on the other. The anhydride property of ozonides has been shown by Rieche by the following reaction.



In their studies of ozonides, the authors have developed a method of quantitative ozonation, determined the amount and identity of any gaseous products of ozonation, determined the effect

of solvents, concentration, and temperature on ozonides, determined dielectric constants and dipole moments of ozonides and the parent unsaturated molecules, determined heats of scission and ozonation, determined the Raman spectra.

It is interesting and perhaps significant that they have found lines in the Raman spectra of ozonides which are characteristic of the aliphatic double bond, although in each case the ray is displaced slightly toward the longer wave lengths than in the parent unsaturated molecule. They have also found lines considered characteristic of peroxides and lines characteristic of anhydrides. Raman spectra data, therefore, link the ozonides with the peroxides and anhydrides.

Briner suggests that the lines found in the region 1630 to 1680 cm^{-1} (region considered characteristic of the aliphatic double bond) are due to the bonding system present in ozonamides. Beyond this suggestion, the authors have drawn no conclusions from their Raman spectra data, dipole moment data and dielectric constant data.

<u>Bibliography</u>:

Briner et al., Helv. Chim. Acta., 22, 224, 587 (1939); 21, 762, 1297, 1312, 357 (1938); 20, 767 (1937); 19, 1163 (1936); 13, 1030 (1930)

Reported by C. M. Himel
November 29, 1939

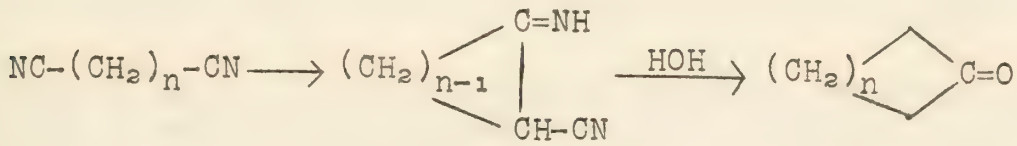
THE SYNTHESIS OF ALICYCLIC KETONES

Dem'yanov and Feofilaktov -- Institute of Organic Chemistry,
Nayk Academy, U.S.S.R.

The first section of this report will deal with the synthesis of the simple alicyclic ketones up to 34 carbon atoms excluding cyclopropanone, whose attempted synthesis will be considered in the second section.

I. Despite the considerable quantity of work which has been done on alicyclic ketones, there are but three methods of any real generality. These will be considered in order of usefulness.

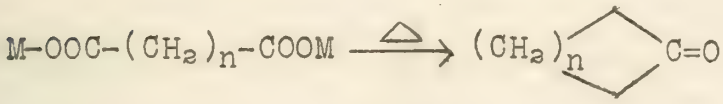
1. Ziegler's method (1)



has been applied where $3 < n < 33$ carbon atoms, excluding 30, 31, and 32 carbon rings. Apparently below five it does not give a monomeric product, but there is no reason suggested for not continuing above 33. Sample yields are as follows:

5-8 carbons in the ring 90-95 per cent, 9- 17 per cent, 10- 37 per cent, 11- 1.35 per cent, 12- 8 per cent, 13- 12.8 per cent, 14- 62 per cent, 15- 60 per cent, 16- 77 per cent, 17- 70 per cent, 18- 82 per cent, 19- 72 per cent, 20- 80 per cent, 22- 83 per cent, 23- 65 per cent, 24- 74 per cent, 25- 64 per cent, 26- 68 per cent, 28- 87 per cent, 29- 76 per cent, and 33- 68 per cent.

2. Ruzicka's method (2), the historical method for 7-, 8-, and 9-membered rings,

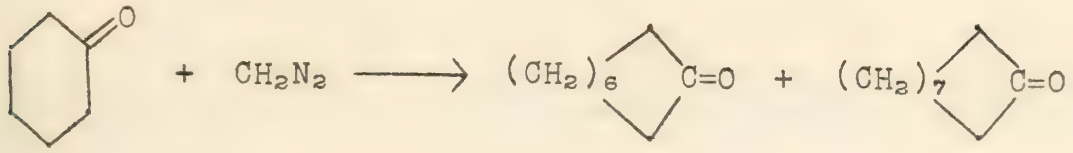


$3 < n < 34$
M is a metal, as Ca, Ba, Th, Yt, Pb, and Ce.

has been used a great deal for synthetic work, but the yields are low above cyclooctanone followed by a slight increase. Like Ziegler's method, it would not produce ketones of less than five members in the ring. Not many yields are given. A few samples are as follows:

Calcium adipate cyclopentanone 43 per cent, thorium 15 per cent, lead 35 per cent. With the higher ketones, however, thorium and yttrium are the only metals which perform satisfactorily, and no general rule can be made for the best metal.

3. Diazomethane expansion (3) has been used up to cyclodecanone. For example,



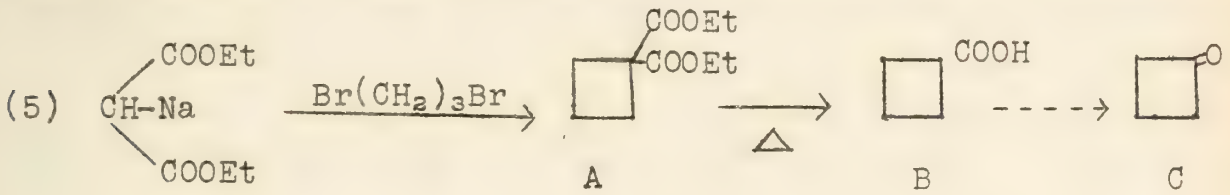
By this method ketene may be expanded to cyclobutanone, the intermediary cyclopropane not being isolated, and so on up to the decanone. Expansion of pentanone has a tendency to go directly to cycloheptanone and cyclooctanone.

Besides these general methods there are many less general and special methods which will be considered by the ketones formed.

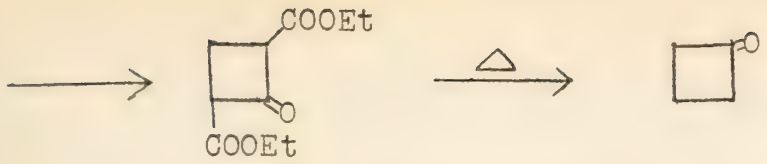
Ketene is made almost entirely by catalytic thermal decomposition of small molecules, particularly acetone, though a "ring closure" by splitting out of HBr or Br_2 has been used on Br-acetaldehyde and Br-acetyl Br, as in closures of 4-, 5-, and 6-membered rings to be discussed in Section II. These methods are to be discussed in a later seminar and will be omitted here.

4. Cyclopropanone will be considered in Section II.

5. Cyclobutanone is made by a wide variety of methods all of which, except the above diazomethane, depend on malonic ester syntheses (5) as follows:



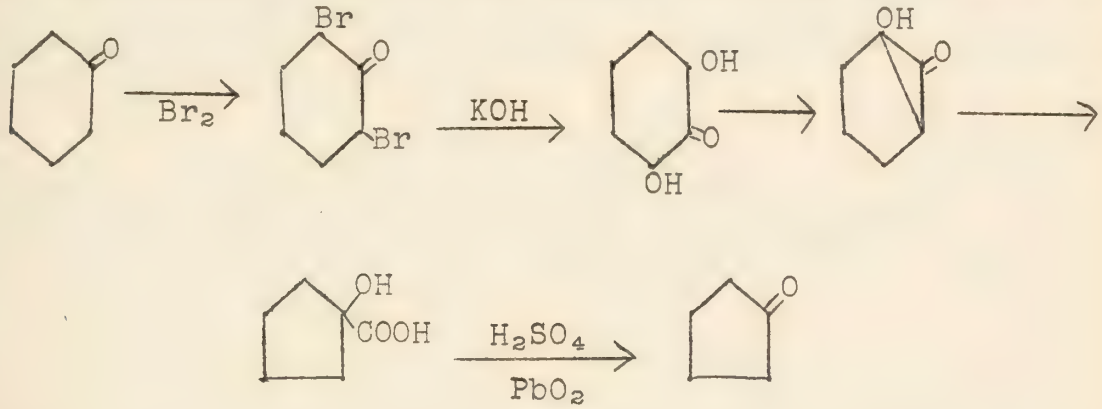
A and B are made into cyclobutanone by several methods: (a) A to its azide to C by hydrolysis; (b) B to its bromide to its α-hydroxide or α-amino derivative followed by decomposition to C; (c) B to its amide followed by Hofmann hypobromite to cyclobutylamine which may be oxidized to C; (d) B's potassium salt electrolyzed to C; (e) B's silver salt coupled by I_2 to cyclobutyl cyclobutane carboxylate with loss of CO_2, followed by splitting to cyclobutyl alcohol and -carboxy acid, followed by oxidation to C; (f) another malonic ester synthesis of interest in that it is also applicable to cyclopentanone and cyclohexanone and is more direct (5f):



Many of these methods have been applied to cyclopropanone derivatives, and some to cyclopropanone, as will be seen in Section II.

6. Cyclopentanone, again, lends itself to many special methods, but it should be remembered that the general methods 1, 2, and 3 are now all available. The other available methods include (a) an adaptation of the salt method; (b) consisting of heating with a metal salt or oxide catalyst, not as generally successful as 1, a new contraction reaction (6b) possibly applicable in other rings, but not used except for this 6 to 5 case as yet.

(6b)



(c) method 5a with $Br(CH_2)_2Br$; (d) a Grignard method, not of general importance or use (6d);

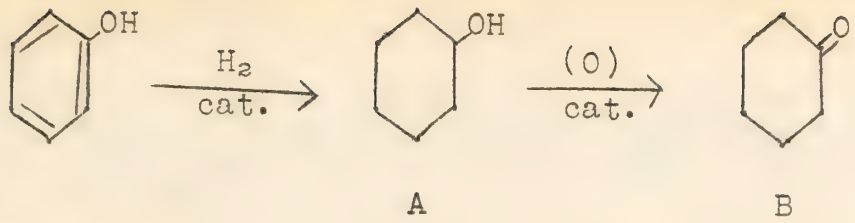
(6d) $Br\text{-}(CH_2)_4\text{-}Br + Mg \xrightarrow{\text{ether}} \xrightarrow{CO_2}$ 

(e) Blanc's method (6e) involving the heating of adipic acid with Ac_2O.

Cyclopentanone is also found naturally in wood and in acetone extractions of certain cellulose products.

7. Cyclohexanone is, perhaps, more common than any other cyclic ketone. It turns up in many degradations and structure determinations. Synthetic methods include (a) 1,2 and its variations, and 3, though as stated above, the last is of very little use; (b) an electrolysis method on cyclohexyl carboxylic potassium salt giving a poor yield, cf. (5d); (c) a method involving the α-bromide of cyclohexyl carboxylic acid followed by a process like those in 5b; (d) Blanc's method (6e) on pimelic acid; (e) reduction from phenol, by far the most important method;

(7e)

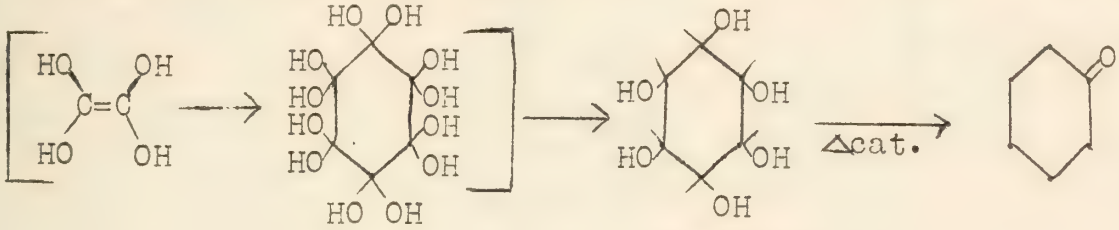


An industrial variation of this involves disproportionation between phenol and A to B; (f) another expansion method

(7f)

(g) a rearrangement of cyclopentyl aldehyde giving a poor yield; (h) oxidation of isonitrocyclohexane by $KMnO_4$ with good yield (not important as yet); (i) a peculiar reaction interesting in that it employs natural inositol:

(7i)



inositol

8. Cycloheptanone or suberone has been known for a long time because of the ease of its production by the calcium salt method (2). Although also made by 1 and 3, it has usually been obtained through 2 from (a) natural cork (8a) which gives suberic acid and (b) from castor oil - saponified to ricinoleic acid, in turn split into suberic and azelaic acids by alkali fusion; (c) it may be obtained from natural tropilene, (8c) Δ^2-cycloheptenone, by catalytic reduction; (d) ring expansion by HCN (7f) is also applicable for expanding hexanone to heptanone.

9. Cyclooctanone is obtainable by 1, 2, or 3, by the HCN expansion (7f) and from natural granitol, a homolog of tropilene, that is, Δ^2-cyclooctenone.

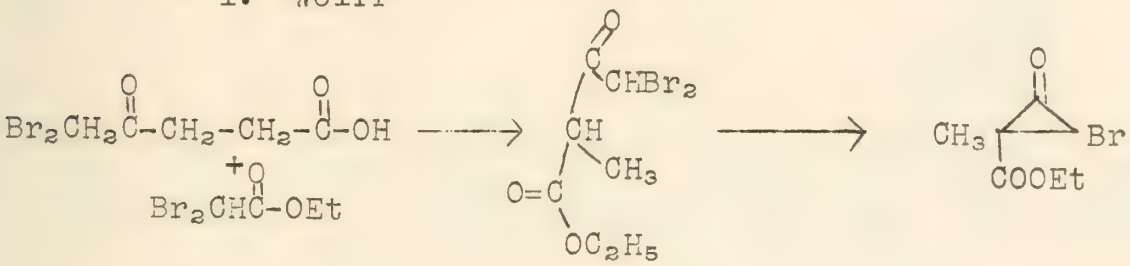
Nine and ten-membered cyclic ketones are obtained by methods 1, 2, or 3.

Ketones of eleven members and up are made by methods 1 and 2 as stated. Seventeen is obtained by hydrogenation of civetone, Δ^9-heptadecenone.

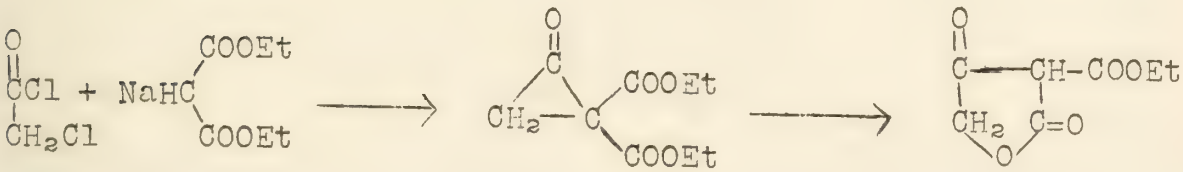
II. Dem'yanov has attempted, in the posthumously published article on which this section is based, to repeat the work of Ingold, who has reported the synthesis of cyclopropanone. The evidence which the article and its bibliography presents makes it quite unlikely that Ingold actually had cyclopropanone.

In all cases where 3-membered ring ketones have been clearly identified there have been gem or other large groups or an adjacent ring of the condensed or spirane type to stabilize the compound. For example:

1. Wolff

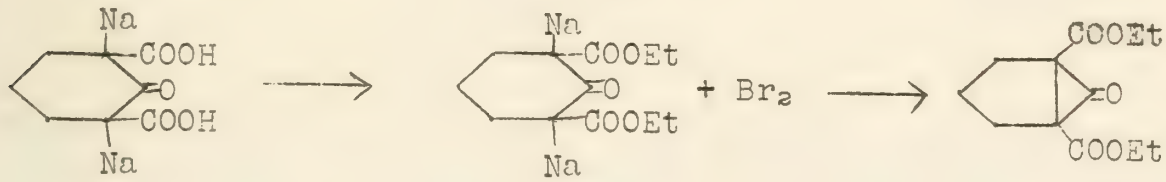


2. Benary

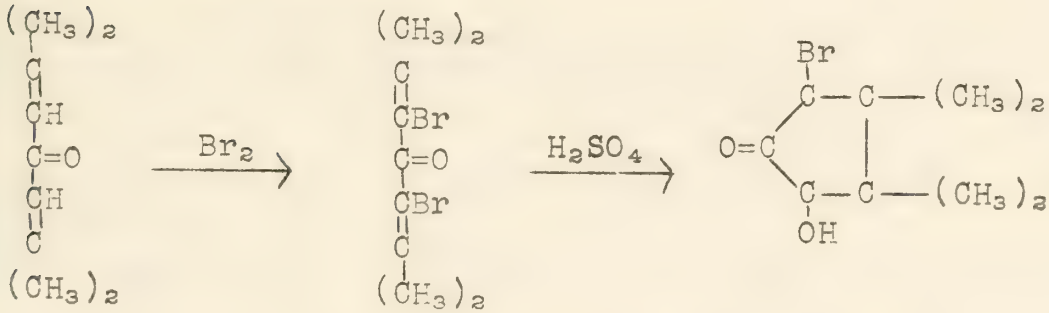


unstable

3. Guha and Seshadriengar have obtained by a synthesis like that shown in Section I (5f) the following series of compounds:

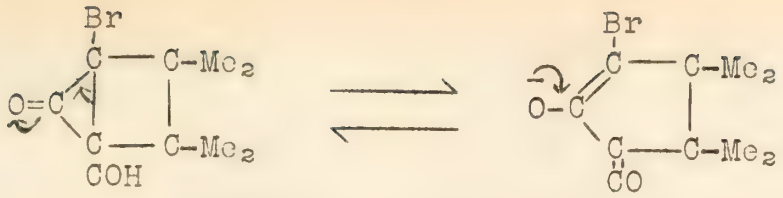


4. Francis and Wilson

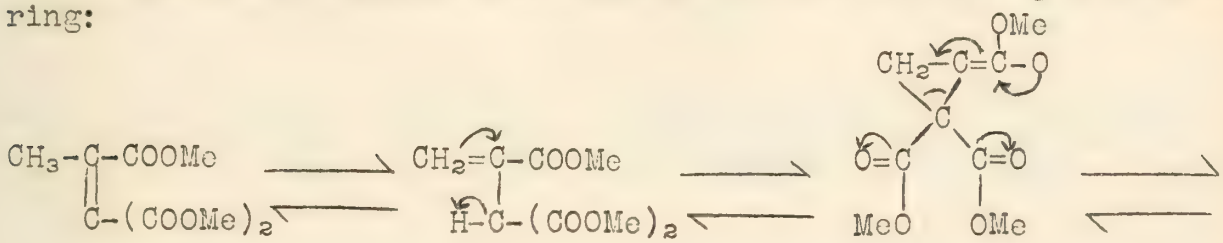


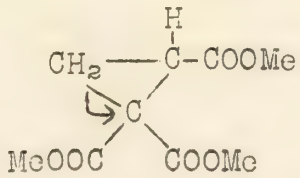
decomposes easily.

Ingold and Shoppee, in regard to the above, declare the compound stabilized by tautomerism:

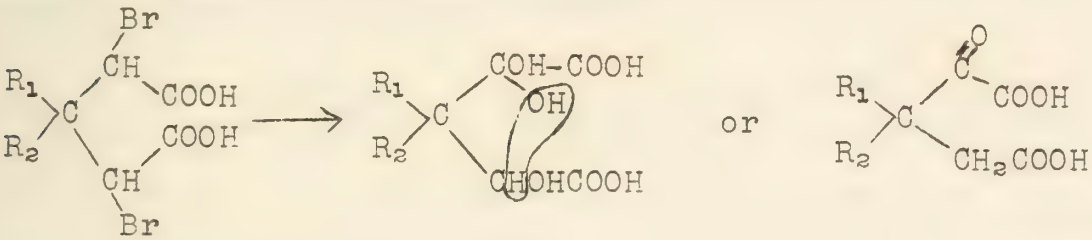


Baker also has postulated tautomerism in the following 3-membered ring:





The importance of steric effects was shown by Thorpe and coworkers who made a series of compounds as follows:



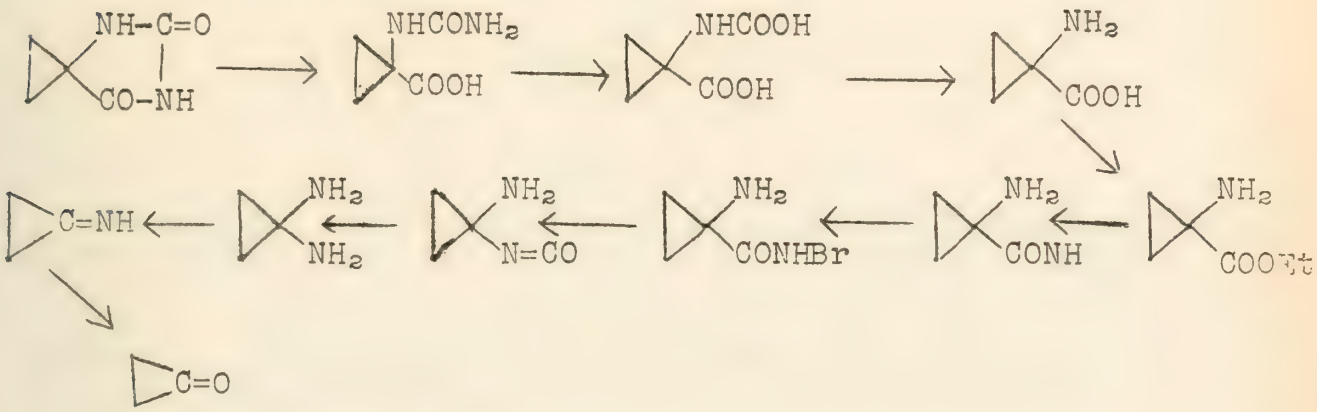
Where Me=R_1=R_2 they obtained no ring closure, with R_1,R_2=cyclohexyl a stable closure was found as shown. With R_1=Me, R_2=Et the ring was fairly stable, with R_1, R_2=Et the 3-membered ring to open-chain ratio was 62 to 38. If R_1=R_2=propyl the ratio became 71 to 21.

Ingold, calculating strain angles in small rings with allowance for gem dimethyl atomic volumes finds:

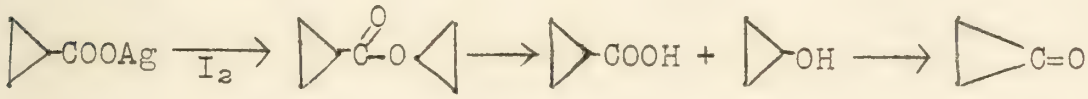
	3-C	4-C	5-C	6-C	7-C rings
Baeyer strain angles	24.7°	9.7°	0.7°	5.3°	--
ΔH formation, cal.	38.1	42.6	16.1	14.3	--
Ingold strain angles	.345	.427	.22	.207	0.730°

Although this is interesting in that it "follows one's intuitive feeling for relative ease of formation of 4, 5, 6, and 7-membered rings," actually ΔH of formation is an indication of stability and not ease of formation. The important thing to this discussion

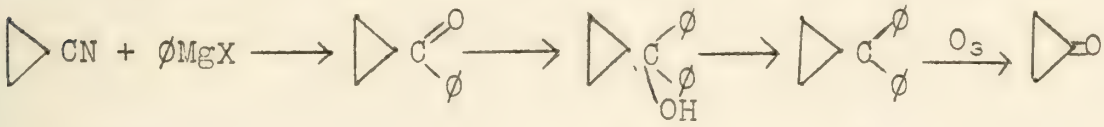
Ingold and coworkers failed to produce cyclopropanone by the following synthesis:



Dem'yanov, who had had much experience with small rings, and Schmitz who had written a thesis on cyclopropanone and cyclopropanol, maintained that Ingold had not made cyclopropanone but probably a dimer or degradation product. For this reason Lipp decided to attempt the synthesis by new methods, customary ring closures being of no use (see Section I, 1 and 2). Degradations of derivatives of cyclopropane and ring closures of acetone gave only mixtures of ketones and alcohols of aliphatic and unsaturated series. Trying to repeat Ingold's work as follows:



he obtained only cyclopropane carboxylic acid and other degradation products. In a synthesis of the following type:



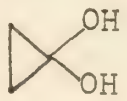
A

he finally succeeded in getting A, but only benzophenone was obtained on ozonolysis.

A diazomethane expansion of ketene (Section 1, 3) led only to cyclobutanone. Another, avoiding excess diazomethane, gave a hemiacetal of cyclopropanone - A- in methanol solution

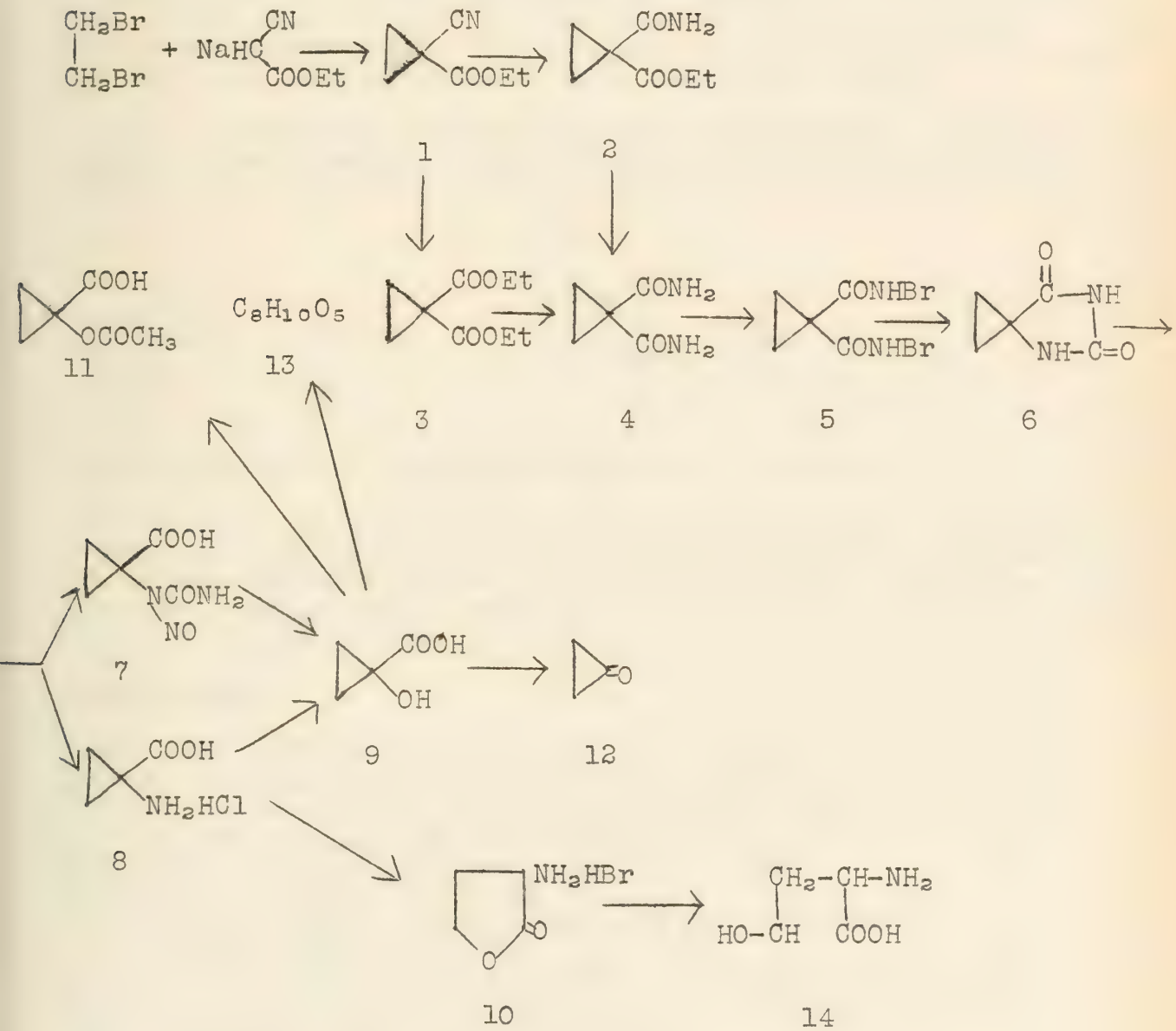
A B

but with semicarbazide in the reaction only B was obtained. In ether solution C was obtained, and this is the nearest authenticated derivative of cyclopropanone. Lipp thus also concluded Ingold to have been mistaken.



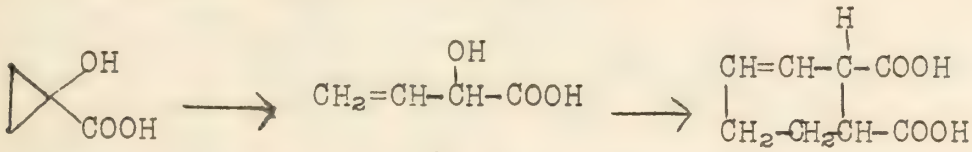
C

Dem'yanov, in the article on which this is based, decided to repeat Ingold's work very carefully by the following scheme:



Compound 1 had been made previously. Compound 4 was to be checked by going both ways from 1. Compound 6 had been made before, and it was split two ways as shown. Either compound 7 or 8 would go to 9 with HNO_2 and 8 was to be split with HBr to 10,

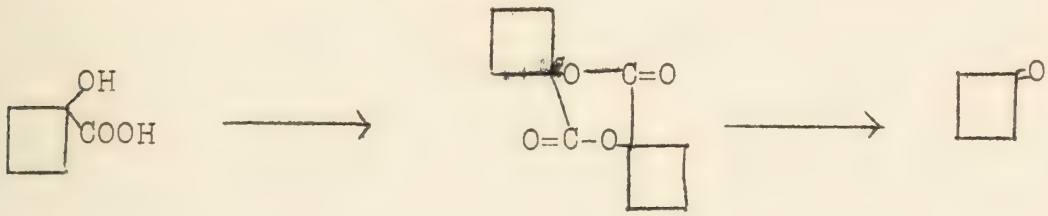
a reaction to which Dem'yanov gives several close analogies. Eleven had been made by Emil Fischer. Nine was to be esterified to 11 and split to 13 for further derivatives. B, below, which would be expected as the product of a ring split from other work on cyclopropane derivatives, is known to give a dimer of empirical formula corresponding to 13 in the table above.



B

Finally 9 was to be decomposed to cyclopropanone (see Section I, 5b). Actually, however, the work was not completed, and Dem'yanov suggests that the structure of the hydroxy acid, which was the last step he reached, will bear more study.

To account for Ingold's supposed cyclopropanone and its semicarbazone he notes first that in previous research on cyclobutanone the following reaction was observed:



A

The intermediate A has been isolated and confirmed.

As this, of course, offers a good explanation of Ingold's ketone and semicarbazone, Dem'yanov and Feofilaktov conclude that all of the evidence points to the nonexistence of Ingold's cyclopropanone, and probable great instability of the compound if, indeed, it exists at all.

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Reported by W. D. Fraser
November 28, 1939

Drake et al. -- University of Maryland

Chevreul was the first investigator to refer to the so-called "cork alcohols" when he described a substance obtained by the alcoholic extraction of cork. Believing it to be a wax, he named it "cerine." Istrati and Ostragovich first showed that there were in reality two substances present, similar in structure, but differing in their solubility in chloroform and in their percentage composition. Istrati named the more soluble of the two "friedelin" in honor of Friedel, who also had investigated these substances.

Thoms thought the material was related to the phytosterols, since he and others obtained color tests characteristic of sterols with these substances. These results, however, were undoubtedly due to the presence of small amounts of impurities, since Drake, et al., failed to obtain the usual sterol color tests when he applied them to carefully purified material, and they did isolate a small amount of a foreign substance, in the course of obtaining pure cerin and friedelin from the crude extract, which gave strong positive sterol tests.

Cerin is sparingly soluble in chloroform, so was obtained in a pure state by fractional crystallizations of the crude extract from chloroform, and finally from benzene. Cerin crystallizes in long silky laths which melt with decomposition at 247-251°. Friedelin, which makes up the bulk of the crude extract, is obtained by concentration of the mother liquors, precipitation with acetone, and purification by esterification and saponification.

Carbon and hydrogen analyses on friedelin indicate an empirical formula of $C_{30}H_{50}O$. The molecular weight of friedelin was determined from the iodine content in the p-iodobenzoate and by finding the saponification equivalents for an homologous series of its esters. The mean value for the molecular weight determined from saponification equivalent data is 425, while that calculated from the formula $C_{30}H_{50}O$ is 426. This establishes the fact that friedelin contains 30 carbon atoms. The low ratio of carbon to hydrogen, the apparent saturated character, and the high melting point indicate a polycyclic structure.

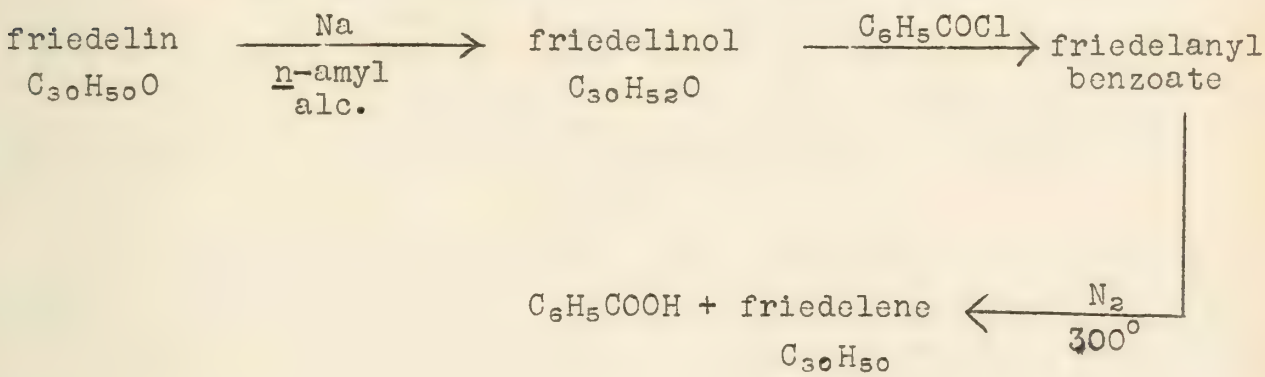
Friedelin is a ketone, as indicated by its ability to form the usual carbonyl derivatives, and the fact that it liberates no CH_4 with CH_3MgI. Esterification apparently takes place through the enol form of the carbonyl group. Clemmensen reduction converts friedelin to a hydrocarbon, $C_{30}H_{52}$. Its saturated character is indicated by the failure to add bromine or hydrogen.

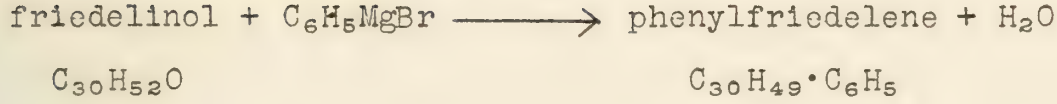
Carbon and hydrogen analyses indicate an empirical formula of $C_{30}H_{50}O_2$ for cerin. Since it reduces to the same hydrocarbon as friedelin, it also must contain 30 carbons. Derivatives of cerin show it to be an hydroxy ketone. It forms the usual carbonyl derivatives. Purdie's reagent converts it to a monomethyl ether, which in turn will form carbonyl derivatives without loss of the methyl group. Reduction with sodium and n-amyl alcohol leads to a dihydroxy compound which is characterized by conversion to the diacetate. A monoacetate may be obtained by acetylation of cerin in

pyridine at room temperatures. The relative position of the carbonyl and hydroxyl group in cerin as compared to that of the carbonyl in friedelin is unknown, since all attempts to convert cerin to friedelin have thus far failed.

Evidence from dehydrogenation studies now indicates that friedelin consists of a polycyclic nucleus containing five fused rings, and is derived from a completely hydrogenated picene. Investigation of degradation products from an attack on the carbonyl group has led to some interesting conclusions.

The following transformations were observed:

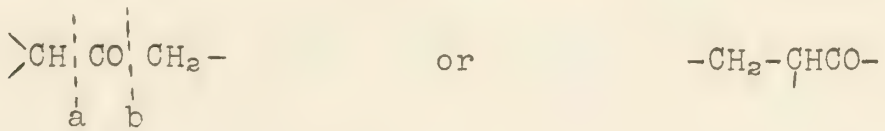




This ready loss of water from the tertiary alcohol, and of benzoic acid from the ester, indicates that there is a hydrogen, probably tertiary, adjacent to the carbonyl. The unsaturated character of the compound produced, namely friedelene, is indicated by the yellow color produced with tetranitromethane.

In addition, friedelene is oxidized by chromic anhydride in glacial acetic acid to a neutral compound, $C_{30}H_{48}O$, which evidently is an unsaturated ketone, since it gives a yellow color with $C(NO_2)_4$, but evolves no CH_4 from CH_3MgI. Inasmuch as no similar compound is obtained by the oxidation of friedelin, it is assumed that the ketone is formed from a methylene group activated by an adjacent C=C bond, a phenomenon quite common in the terpene series.

These facts would then indicate a grouping:



I II

Subsequent data shows I to be the proper arrangement.

Friedelin (III) is oxidized by chromic anhydride in glacial acetic acid mainly to a keto acid, $C_{30}H_{50}O_3$, friedonic acid (XII). This formula is borne out by carbon and hydrogen analyses, neutral equivalents, and saponification equivalents of its methyl ester. The formation of this keto acid indicates the presence of some substituent on the carbon atom adjacent to the carbonyl group. Although it has not been possible to prepare derivatives of this acid by replacement of the carbonyl oxygen, it can be reduced to a neutral substance, $C_{30}H_{50}O_2$, the lactone of an hydroxy acid for which the name friedolo lactone has been proposed (XV).

Besides friedonic acid, oxidation of friedelin yields a small amount of a keto acid containing 29 carbons. This is separated by conversion to the lactone, $C_{29}H_{48}O_2$, norfriedolo lactone (X). The simplest interpretation of these reactions is that structure I is cleaved at a and b, forming respectively friedonic acid and a dibasic acid (VIII) which, because it contains a $>CH-$ group adjacent to a carbonyl, is very easily degraded further, yielding norfriedonic acid (IX), as indicated.

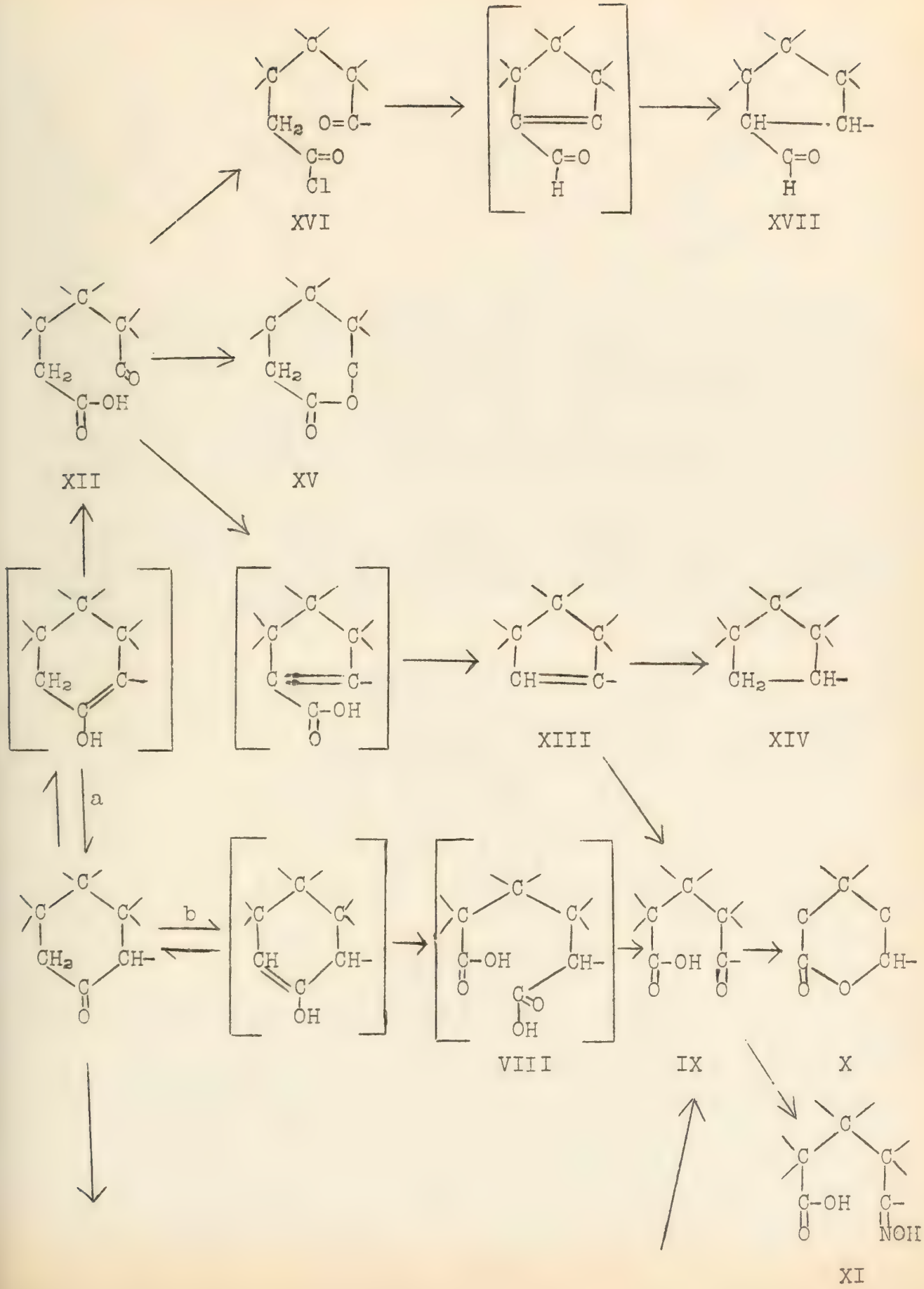
In addition to friedelenone (VI), oxidation of friedelene (V) yields a small acidic fraction which, by reduction, yields norfriedolo lactone, identical with the compound obtained by oxidation of friedelin. Norfriedonic acid is formed, then, from friedelenone by cleavage of the double bond and further degradation of the α-keto acid (VII) produced. This indicates that the CH_2 group in friedelin must be next to the carbonyl, and not as in structure II.

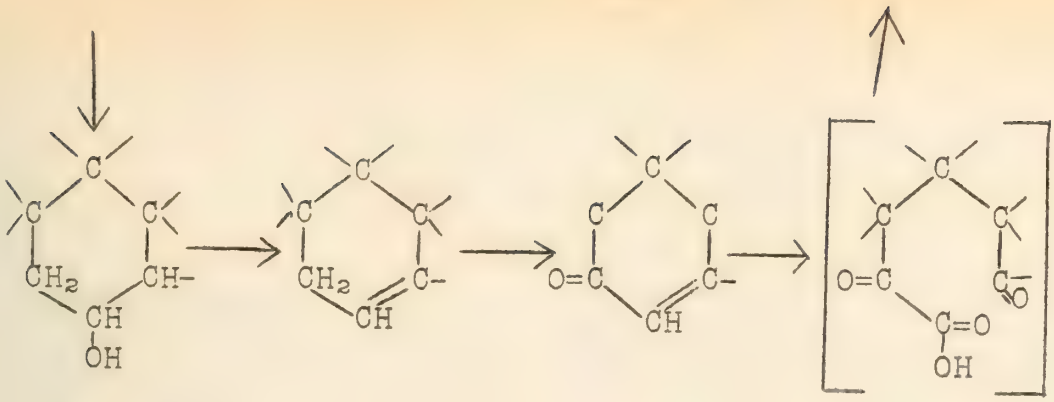
Inability to obtain carbonyl derivatives from friedonic acid prompted Drake et al. to secure further evidence for the presence of a keto group in the acid. When friedonic acid is heated at 250° in a nitrogen atmosphere, water and carbon dioxide are lost with the formation of norfriedelene (XIII), which gives a strong test for unsaturation with $C(NO_2)_4$ and absorbs one mole of hydrogen to form norfriedelone (XIV).

Oxidation of norfriedelene with $KMnO_4$ in glacial acetic acid produces norfriedonic acid (IX), differing from friedonic acid by a CH_2 group, and by its ability to form the usual carbonyl derivatives (XI). This ability of norfriedonic acid and its esters to form carbonyl derivatives indicates clearly that some interaction of carbonyl and carboxyl groups is responsible for the inability of friedonic acid and its esters to yield such derivatives.

Friedonic acid also yields a noncrystalline acid chloride (XVI), with thionyl chloride, which can be reduced to a new compound, $C_{30}H_{50}O$, isomeric with friedelin. It differs from friedelin in being easily oxidized to an acid with the same number of carbon and only two oxygen atoms, and also in regard to the reactivity of its carbonyl group. These facts indicate that a saturated aldehyde, norfriedelanyl formaldehyde (XVII), is formed as shown. All the foregoing data, then, seems to point quite logically to an epsilon-keto acid structure for friedonic acid, with the carbonyl group highly sterically hindered.

Dehydrogenation studies were carried out with selenium on friedelinol (IV) rather than friedelin itself, since friedelin,

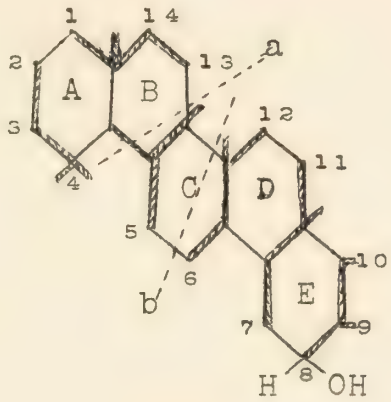

XVI
XVII
XII
XV
XIII
XIV
a
b
VIII
IX
X
XI



IV V VI VII

like most ketones whose carbonyl forms part of a ring system, gives products too complex and too different from the original nuclear structure to be satisfactory. Products obtained are 1,2,7-trimethylnaphthalene (sapotalene), 1,2,8-trimethylphenanthrene, a hydrocarbon, $C_{25}H_{20}$ or $C_{24}H_{18}$, apparently identical with a polymethyl picene isolated by Ruzicka from dehydrogenation products of a number of triterpenes, and a liquid hydrocarbon, $C_{11}H_{20}$, which has the properties of an alkyl substituted cyclohexene.

The evidence given by Ruzicka in support of a picene nucleus in the hydrocarbon $C_{25}H_{20}$ is quite conclusive, so that cerin and friedelin must contain a pentacyclic nucleus of the hydrogenated picene type. A tentative formula (XVIII) has been prepared for friedelinol by Drake:



XVIII

in which heavy lines represent isoprene nuclei.

Cleavage of the molecule at a would result in the formation of 1,2,8-phenanthrene and another substance with 11 carbons, corresponding to $C_{11}H_{20}$, which apparently is a polyalkyl cyclohexene. A small amount of such a substance was obtained having properties which would be expected of this type of compound. Cleavage at b and migration of a CH_3 group from 4 to 3 would result in the formation of sapotalene. Similar migration of methyl groups are known to occur. The location of the OH group is based on the results of the oxidative studies previously described.

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Reported by F. Grosser
December 6, 1939

THE CHEMISTRY OF THE CARYOPHYLLENES

Ruzicka -- Organisch-Chemisches Laboratorium
der Eidg. Techn. Hochschule, Zurich
Ramage and Simonsen — University College of
North Wales, Bangor, England

Caryophyllene is a mixture of sesquiterpenes obtained from oil of clove stems. At present this mixture is thought to consist of three isomeric hydrocarbons possessing the empirical formula $C_{15}H_{24}$. Early workers prepared crystalline nitroso chlorides, and nitrosites and were able to obtain three different derivatives which were named as derived from α-, β-, and γ-caryophyllene. The β-isomer is now thought to make up the bulk of the mixture, the γ-isomer is present in next largest amounts, and the α- is present in small quantities only. α-Caryophyllene is said to be identical with humulene which is obtained from oil of hops.

Caryophyllene contains two double bonds, and practically the only attack available for the determination of the structure is through the oxidation of these bonds and degradation of the products obtained. Ozonolysis yields several products which have been examined separately. The two given below are the main products of the ozonization.

$$\text{Caryophyllene (I)} \xrightarrow{O_3} \begin{array}{ll} C_{14}H_{22}O_4 & - \text{ a diketocarboxylic acid} \\ C_{11}H_{18}O_3 & - \text{ a ketocarboxylic acid} \end{array}$$

Both of these acids yield the same products on oxidation with nitric acid.

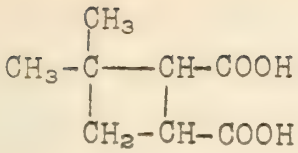
$$\left.\begin{array}{l} C_{14}H_{22}O_4 \\ C_{11}H_{18}O_3 \end{array}\right\} \xrightarrow[\text{ox.}]{HNO_3} \begin{array}{ll} C_9H_{14}O_4 & - \text{ caryophyllenic acid (III)} \\ C_6H_{10}O_4 & - \text{ αα-dimethyl succinic acid (IV)} \\ C_8H_{12}O_4 & - \text{ norcaryophyllenic acid (II)} \end{array}$$

$$\text{II} \xrightarrow[PCl_5]{Br_2} \xrightarrow[KOH]{EtOH} \text{dehydronorcaryophyllenic acid} \xrightarrow{O_3} \underset{\text{keto acid}}{C_7H_{10}O_5}$$

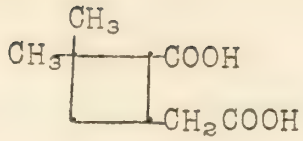
$$\xrightarrow{H_2O_2} \text{IV}$$

II readily formed an anhydride when treated with acetic anhydride and so must be the cis form of 3,3-dimethyl-1,2-dicarboxy cyclobutane. This compound has been synthesized and found to be identical with the norcaryophyllenic acid obtained from caryophyllene.

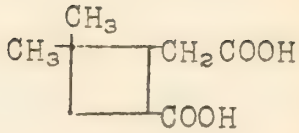
Caryophyllenic acid (III) was thus seen to possess structure IIIa or IIIb. These two may be distinguished only by the complete synthesis of III which has not yet been accomplished.



II



IIIa

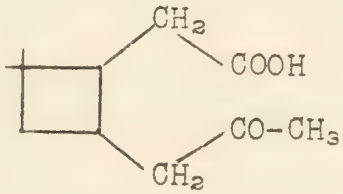


IIIb

The keto acid, $C_{11}H_{18}O_3$ (V), when treated with bromine and alkali is oxidized to a dibasic acid (VI) which is readily cyclized to a ketone.

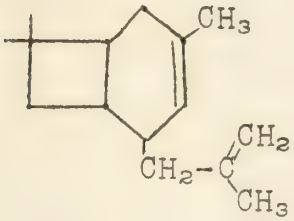
$$C_{11}H_{18}O_3\ (V) \xrightarrow{NaOBr} C_{10}H_{16}O_4\ (VI) \xrightarrow{Ac_2O} C_9H_{14}O$$

VI is homocaryophyllenic acid, hence the keto acid (V) must possess the following structure.

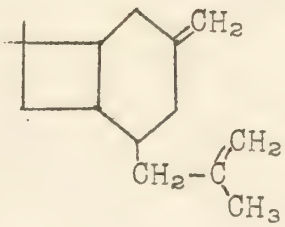


V

On the basis of these results the following structure has been proposed for β-caryophyllene (Ia). γ-Caryophyllene yields only neutral products upon ozonolysis and might be Ib.



Ia

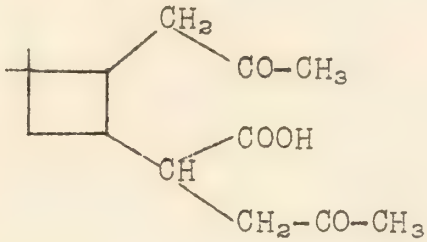


Ib

I can be hydrated easily to form caryophyllene alcohol, which on dehydration yields a new hydrocarbon which is isomeric with I and has been named clovene. I is also converted into clovene by heating with mineral acids. Clovene is evidently a tricyclic hydrocarbon and upon oxidation yields a C_{15} dibasic acid which possesses an exceptional stability and inertness toward any degradation reagents. No satisfactory structure has yet been proposed for clovene and clovenic acid. The formation of clovene from I might involve a shift of a double bond, an opening of the four-membered ring, or both along with the cyclization.

When treated with maleic anhydride about 70 per cent of I reacts to form an addition compound, while 30 per cent refuses to react. This offers another demonstration of the fact that the crude caryophyllene is a mixture of hydrocarbons. The maleic anhydride addition product obtained is fully saturated. No good structure or mechanism of formation for this can be suggested.

The diketocarboxylic $C_{14}H_{22}O_4$ obtained on ozonolysis of I may be represented by structure VII.

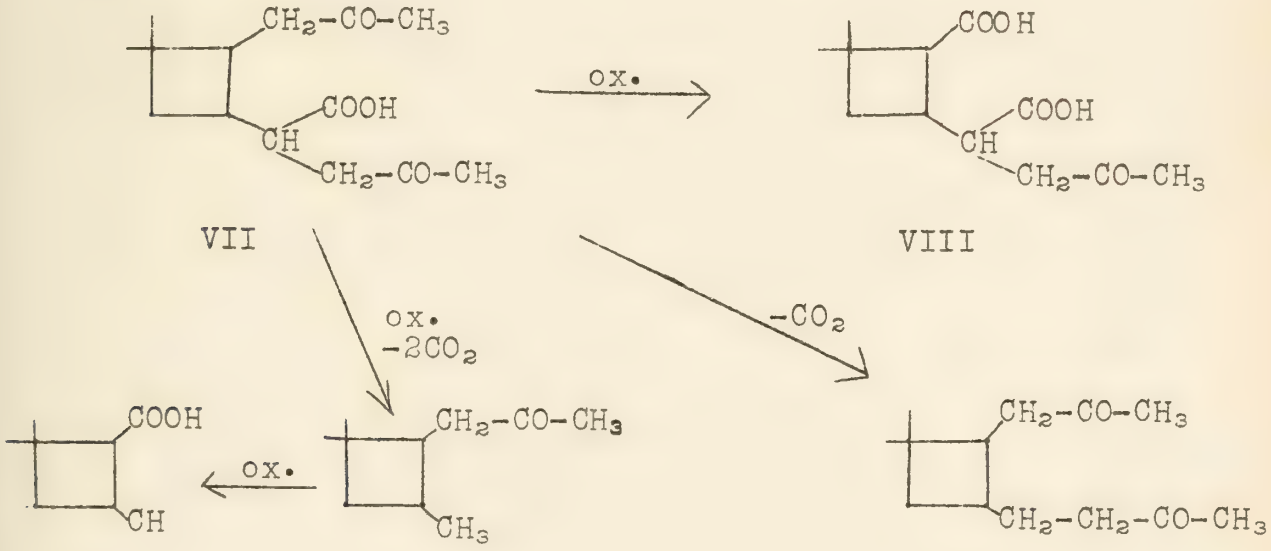


VII

In addition to VII and V the following products have been isolated from the ozonolysis mixture:

$C_{12}H_{18}O_5$ (VIII), a ketodicarboxylic acid;
$C_{12}H_{20}O_2$ (IX), a diketone; $C_{10}H_{18}O$ (X), a ketone;
$C_8H_{14}O_2$ (XI), an acid.

These products may all be satisfactorily accounted for as coming from VII as follows:

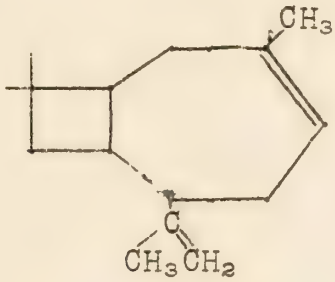


VII VIII

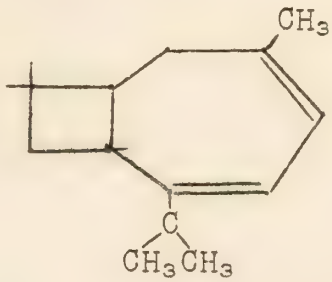
XI X IX

Rydon has recently suggested that structure Ia which was proposed by Ruzicka is not wholly satisfactory, and has presented an alternative structure (Ic). The azulene structure (condensed 4- and 7-membered rings) previously has been found in nature among the terpenes and its structure has been proved by synthesis. This structure (Ic) fulfills most of the facts known about the decomposition products of caryophyllene (except the formation of V)

and has many points in its favor. A double bond isomer of it (Id) may explain the formation of clovene and its oxidation to a C_{15} dicarboxylic acid.

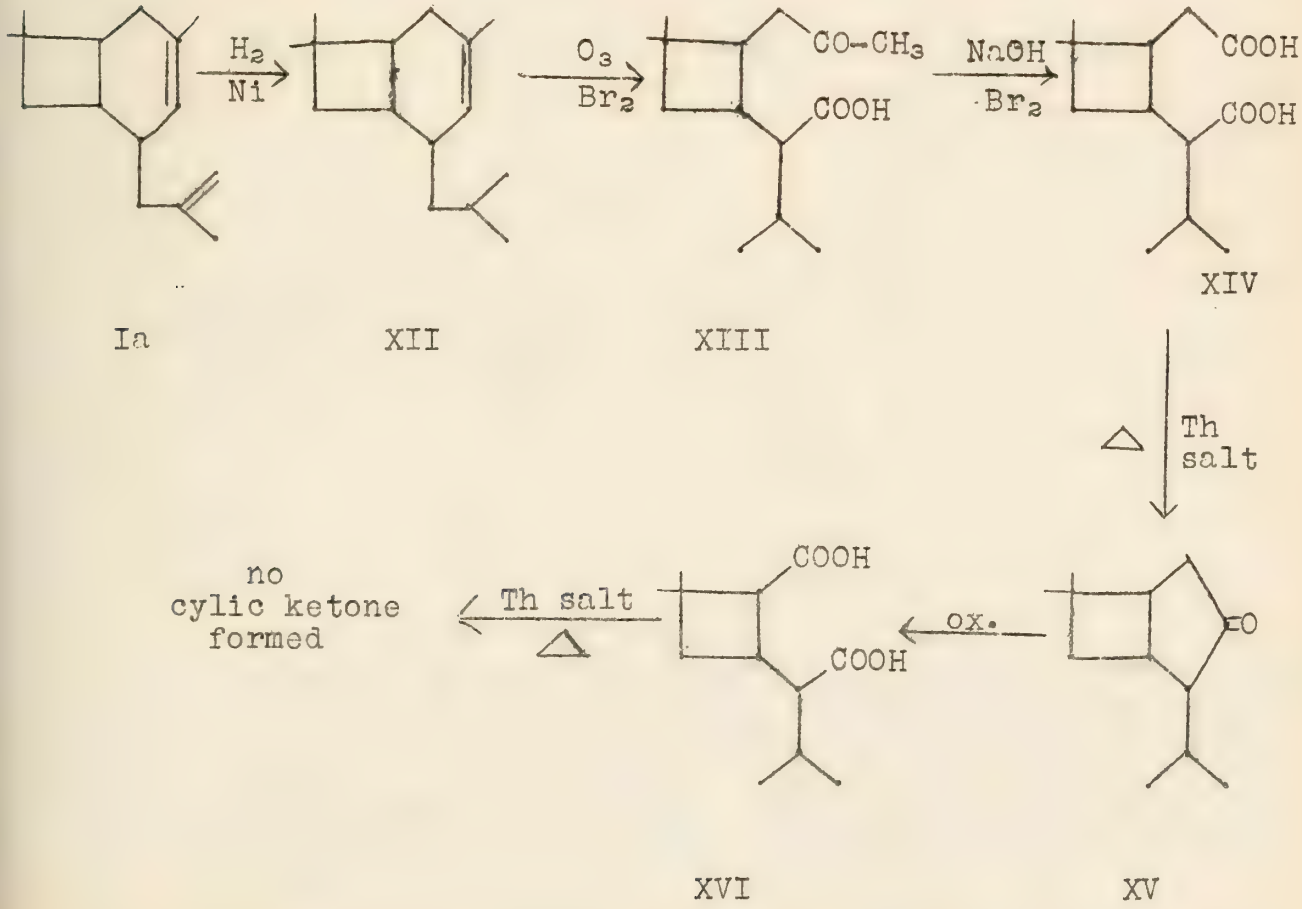


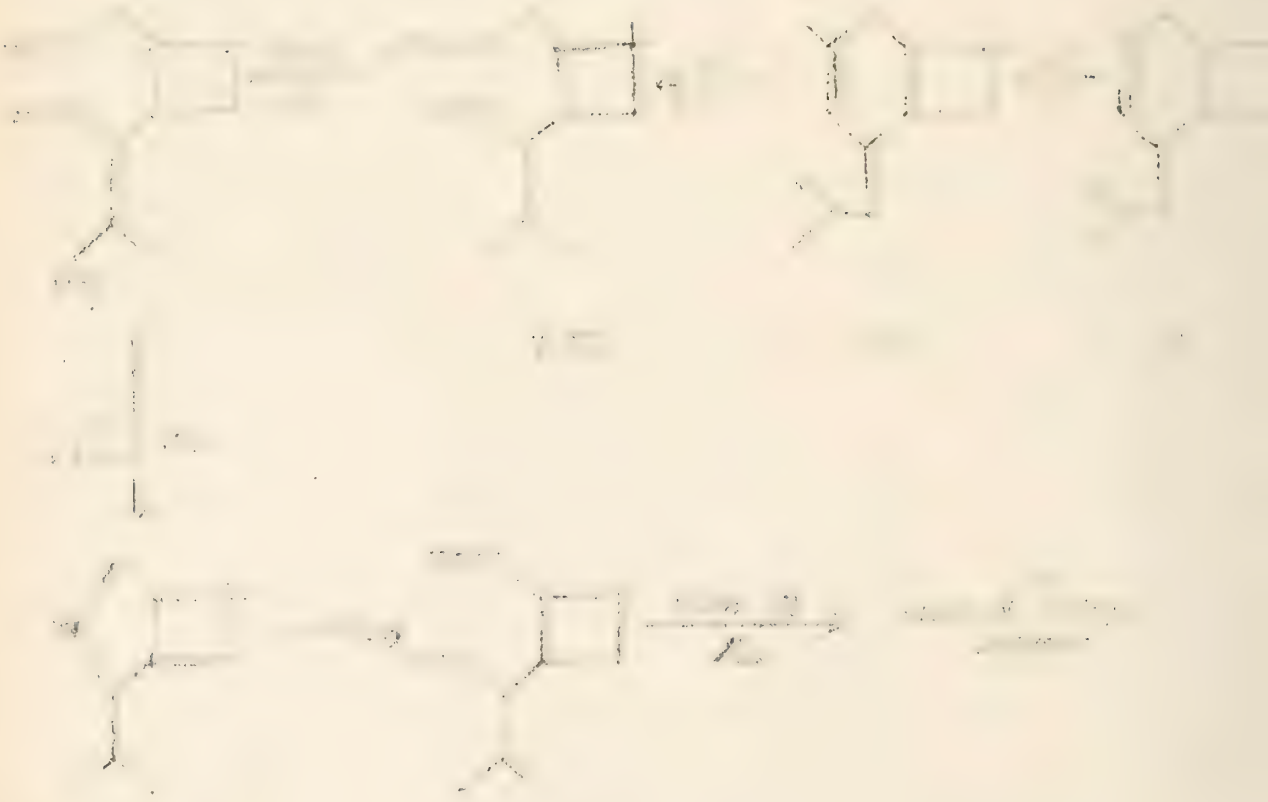
Ic

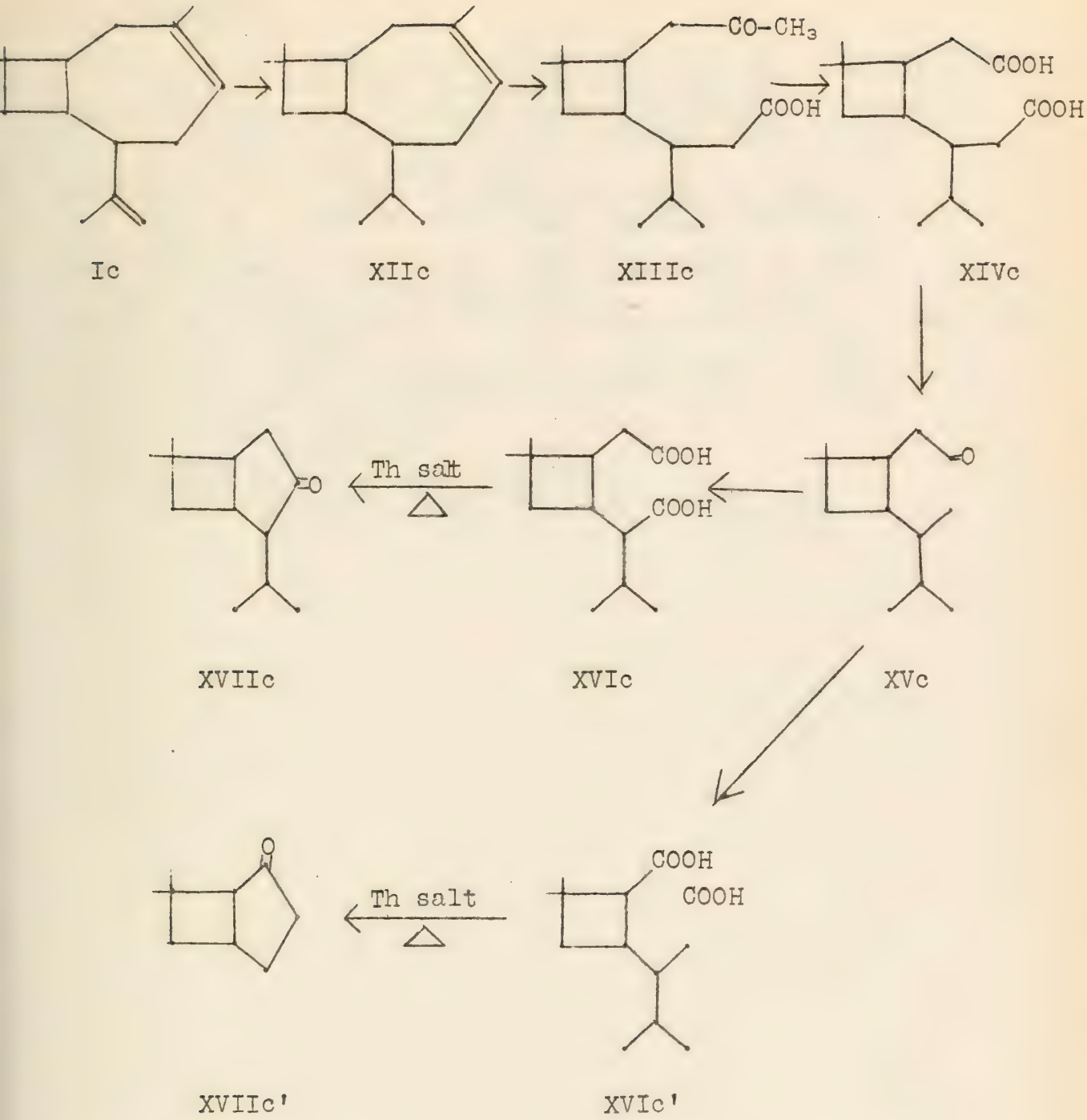


Id

The degradation of dihydrocaryophyllene has been undertaken by Ruzicka in the hope that more light would be thrown upon the skeleton of the caryophyllenes. The following series of reactions was carried out in the expectation that one of the two structures might be proved to be correct.

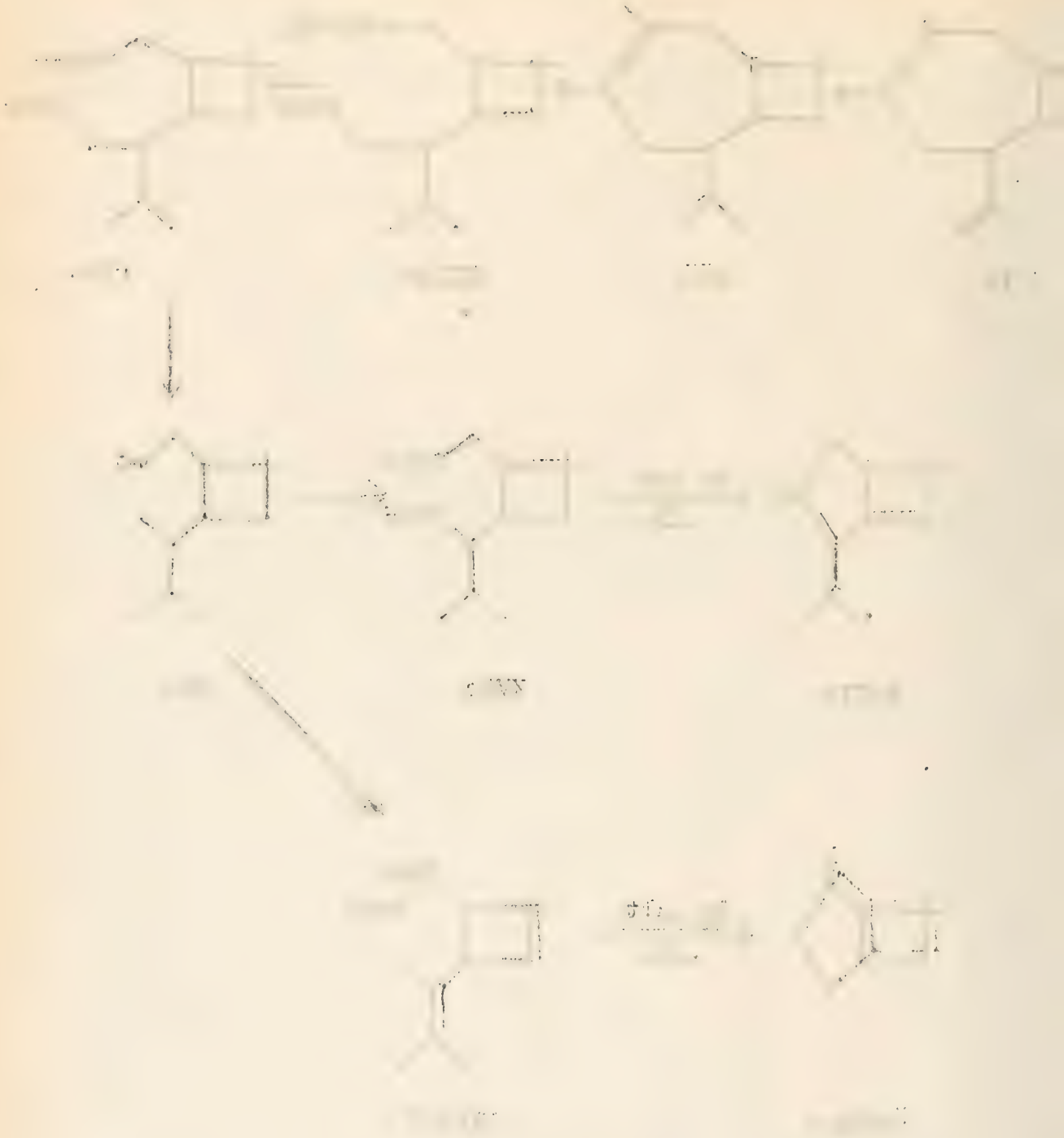






If structure Ia were the correct one the final product would be XVI, a substituted glutaric acid, which could not be converted into a cyclic ketone. If Ic were the true structure the final product would be a cyclic ketone, $C_{12}H_{20}O$. Ruzicka actually obtained a small amount of a ketone $C_{12}H_{20}O$ as the semicarbazone. He concluded that at least a part of the caryophyllene mixture existed as the structure proposed by Rydon.

In a more recent article Ramag and Simonsen claim results showing that most of the caryophyllene mixture has the structure suggested by Ruzicka.



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Ramag and Simonsen, J. Chem. Soc., 1208 (1938); 73 (1937); 741 (1936); 532 (1935); 1581 (1935); 1806 (1934); Chem. and Ind., 1939, 447.
E. Deussen, Ann., 495, 233; 388, 136; 369, 41; 359, 245; 356, 1; J. prakt. chem., 145, 31; 122, 261; 117, 773; 114, 63.
Semmler and Mayer, Ber., 45, 1384; 44, 3657; 43, 3451.
Haarman, Ber., 43, 1505; 42, 1062.
Robertson and Henderson, J. Chem. Soc., 1971 (1930); 1368 (1939); 62, 164 (1926)
Rydon, Chem. and Ind., 1938, 123; 1935, 557; J. Chem. Soc., 1340 (1937); 593 (1936).
Chapman, ibid., 1928, 785.
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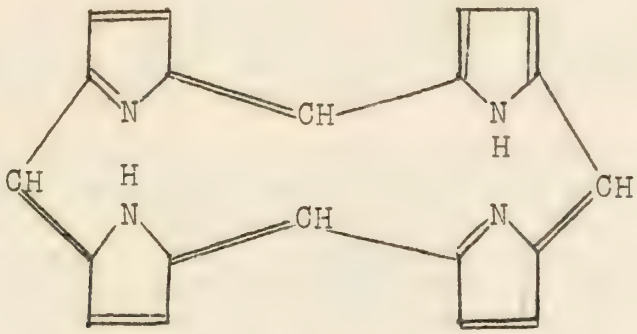
St. Pfau and Plattner, Helv. Chim. Acta., 20, 224.

Reported by M. D. Armstrong
December 6, 1939

THE SYNTHESIS OF A DIIMIDOPORPHYRIN

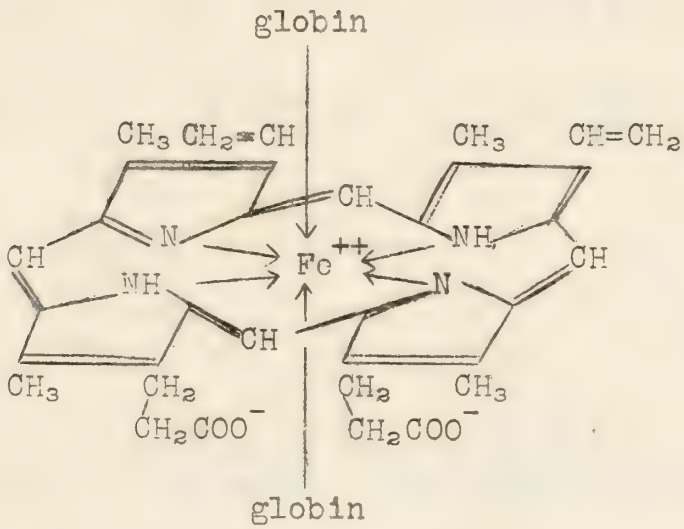
Hans Fischer and coworkers, der
Technische Hochscule, München

The skeleton of natural porphyrins is a planar cycle of four pyrrole nuclei linked between their alpha-positions by methine groups.



Many molecules of this type, for example, chlorophyll and hemoglobin, have been characterized and synthesized. Fischer's recent book, describing this research, also records the properties and chemistry of many pyrrole derivatives which he encountered as intermediates.

In living organisms the porphyrin skeleton occurs linked by covalent bonds to a central metallic ion. The iron of hemoglobin, for example, is present in an octahedral complex with four coordination positions occupied by hematoporphyrin and two by the protein, globin.

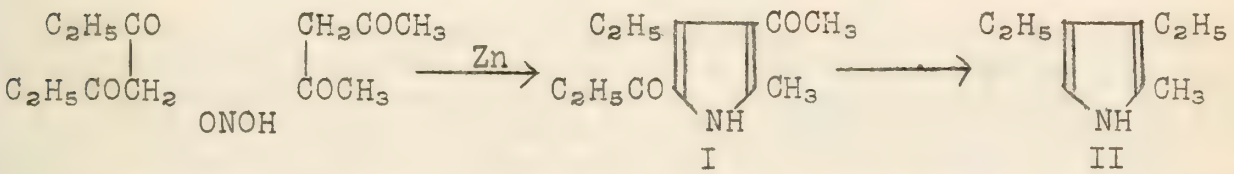


Porphyrins in which nitrogen atoms replace the bridging methine groups of the natural porphyrins are called imidoporphyrins. Thus, the phthallocyanine dyes which contain four bridging nitrogen atoms are called tetraimidoporphyrins. Replacing the methine groups by nitrogen atoms one by one, Fischer has studied the variation of basicity, absorption spectrum and other properties.

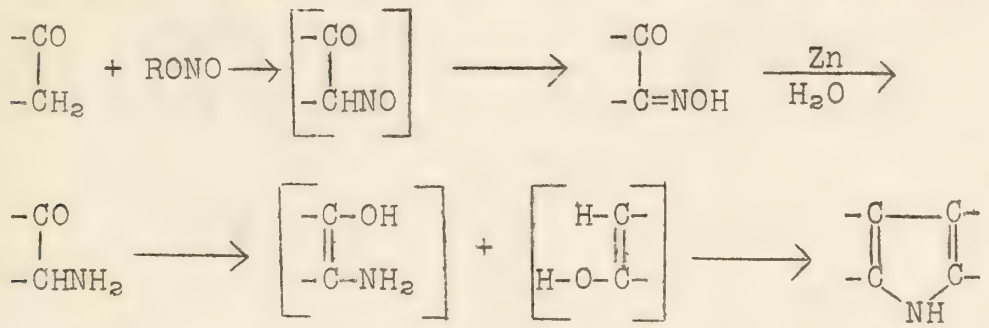
The article which is the basis of this paper describes the synthesis of a diimidoporphyrin. Here the bridging groups are two nitrogen atoms and two methine groups.

The compound which Fischer wished was the diimidoporphyrin containing eight ethyl groups in the beta-positions of the pyrrole nuclei. The bridge nitrogen atoms were to be arranged symmetrically about the center of the porphyrin skeleton. The intermediate to be synthesized was, therefore, 3,4-diethylpyrrole with alpha-substituents suitable for conversion to the bridges. Selecting the methyl and amino groups as the simplest substituents, Fischer set out to make 2-methyl-3,4-diethyl-5-aminopyrrole.

Dipropionylmethane and diacetylmethane were condensed by the reductive Knorr synthesis to 2-methyl-3-acetyl-4-ethyl-5-propionylpyrrole (I). This important synthesis will be discussed in the next paragraph. Since alpha-groups are less firmly held to the pyrrole nucleus than are beta-groups, careful treatment of I with sulfuric acid removed only the propionyl group. The acetyl group was then reduced to an ethyl group by the Wolff-Kishner method, that is, by heating of the hydrazone of the ketone with sodium ethoxide; 2-methyl-3,4-diethylpyrrole (II) resulted.



The first intermediate in a general Knorr synthesis is the isonitroso ketone formed by action of a nitrous ester on a ketone. Subsequent reduction by zinc produces the alpha-amino ketone. This condenses with a second ketone to yield a pyrrole.

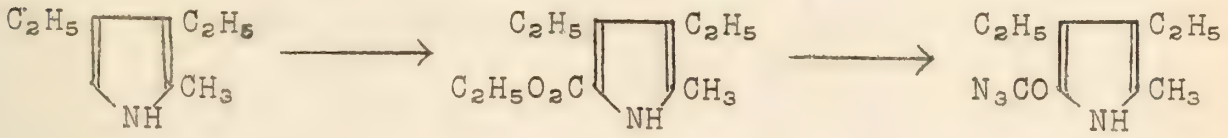


If diketones are used, as in this preparation, nitrous acid may be substituted for its ester. The yields obtained are much better.

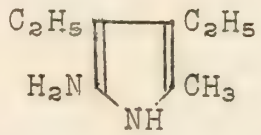
Introduction of the alpha-nitrogen was first attempted by coupling of II with benzenediazonium chloride. The azo compound was obtained but the attempt to reduce it catalytically failed to yield the desired amine.

An indirect attack was begun by introduction of the carbethoxy

group into the alpha-position of II. Heating of the ester (III) with hydrazine yielded the hydrazide which nitrous acid converted to the azide (IV).



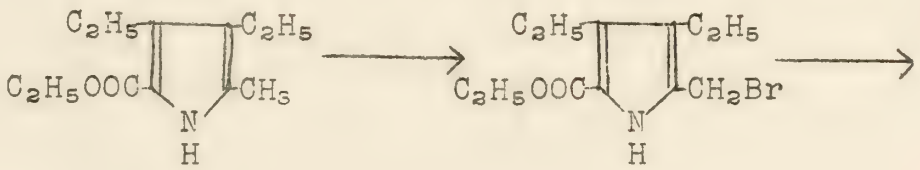
II III IV



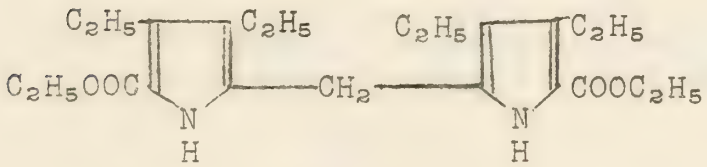
V

Hydrolysis of the azide in 50 per cent acetic acid yielded the desired amine (V).

Before the proper means of hydrolyzing the azide was discovered, the diimidoporphyrin was obtained from the intermediates III and IV. The ester (III) was converted to an alpha-bromomethyl derivative (VI) which could be coupled to the pyrromethane (VII) by boiling in methanol. After hydrolysis of the ester links, bromine-acetic acid treatment caused oxidation to the pyrromethene (VIII) and substitution of bromine atoms for the carboxyl groups. The resultant pyrromethene (IX) could be coupled to the desired imidoporphyrin (X) by treatment with ammonia.

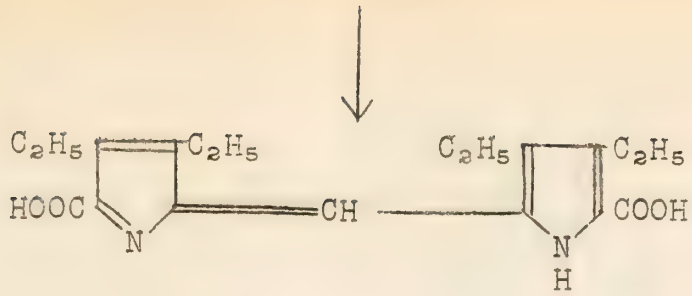


III VI

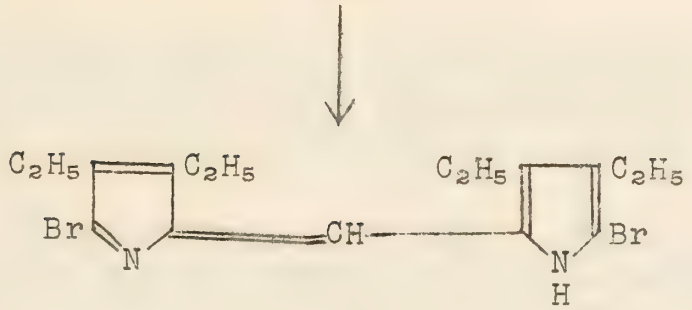


VII

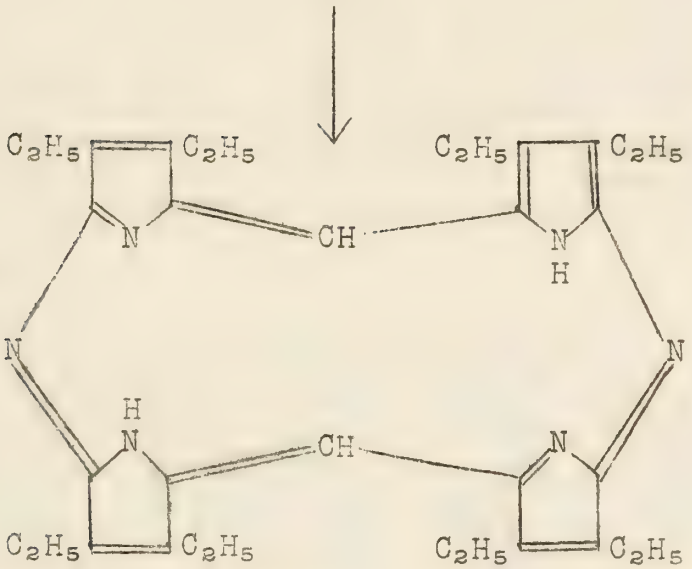
↓



VIII

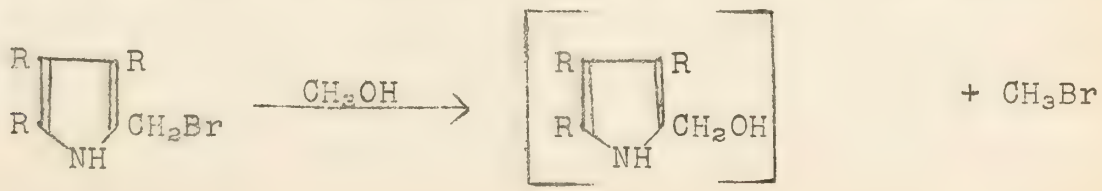


IX

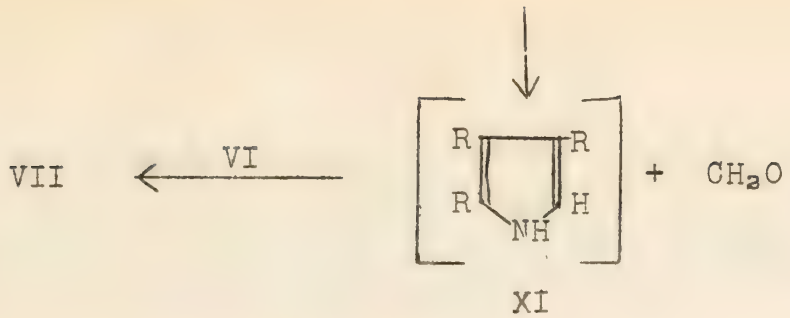


X

Conversion of the bromomethyl derivative (VI) to the pyrromethane (VII) involves the removal of methylene bromide. Fischer writes the following equations to suggest how this may occur.



VI X



The following evidence is in support of this mechanism. Methyl bromide is noted during reaction. alpha-Substituted pyrroles such as X are known to couple with alpha-bromomethyl pyrroles such as VI under the conditions which are used for the conversion of VI to VII.

The alternative preparation began with the azide (IV). Use of methanol as the solvent during the Curtius degradation permitted conversion of the intermediate isocyanate into the methyl-urethan. This product is unusual in that it contains three oxygen atoms. Although the position of the additional oxygen atom is not known, there is little doubt that it exists for the "urethan" is a colorless, crystalline compound whose analysis checks closely for three oxygen atoms. Some half a dozen other "auto-oxidized urethans" of like antecedents are similarly characterized. Heating of this urethan with phenylhydrazine converted it directly to diimidoporphyrin. This product could be separated into two isomers by differential extraction with hydrochloric acid.

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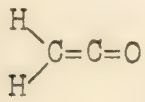
Reported by John Marsh
December 13, 1939

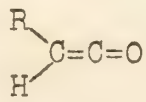
REACTIONS OF KETENES

Staudinger -- Strassburg

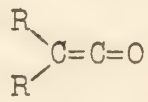
The ketenes are a class of compounds which formally at least have structures which look like unsaturated ketones, whence the name. The formula of ketene itself contains two hydrogen atoms. By a replacement of one or both of these by R groups, two main types of products are obtained. These have been called aldoketenes and ketoketenes, respectively.



ketene



aldoketene

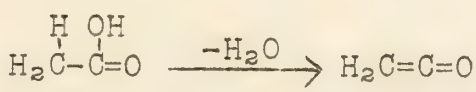


ketoketene

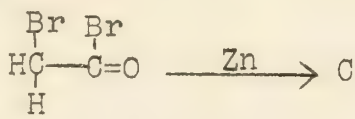
The ethylenic linkage of the ketenes shows all of the characteristics of a genuine ethylenic bond in undergoing simple addition reactions. In these additions it is thought that those addends which are characteristic for the carbon-carbon linkage add to that linkage, while those addends which are characteristic for the carbonyl add to it and the latter addition is followed by ketonization.

The ketene carbonyl group resembles the carbonyl of a carboxyl group in that it undergoes no reaction with aldehyde or ketone reagents.

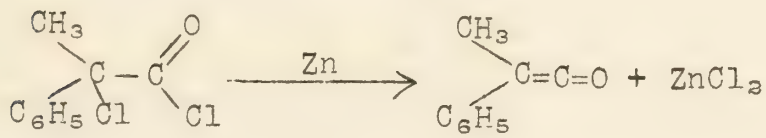
The best interpretation of the character of the ketenes is that they be regarded as internal anhydrides of the corresponding acids. Thus:



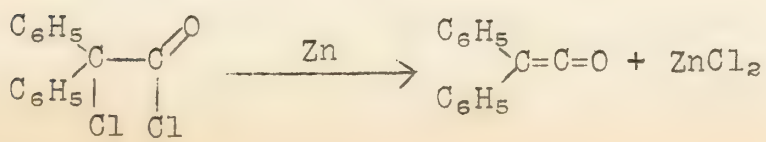
Methods of Preparation.--The nearest to a general method of preparation is in the removal of halogen from α-halogen substituted acyl halides.



12 per cent



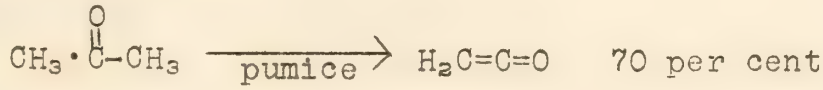
80 per cent



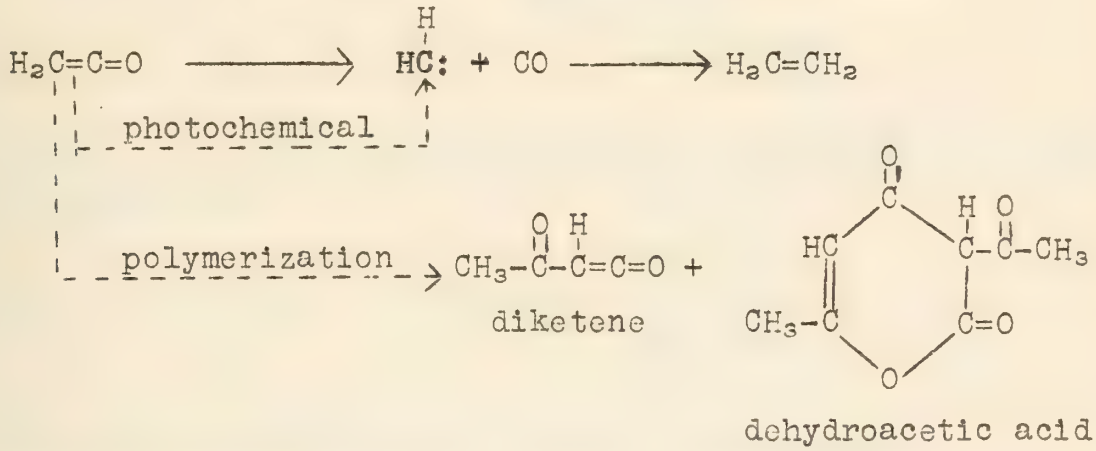
95 per cent

Aromatic substituents in the acyl halides favor the reaction.

The best method for the preparation of ketene itself is Hurd's pyrolysis of acetone.

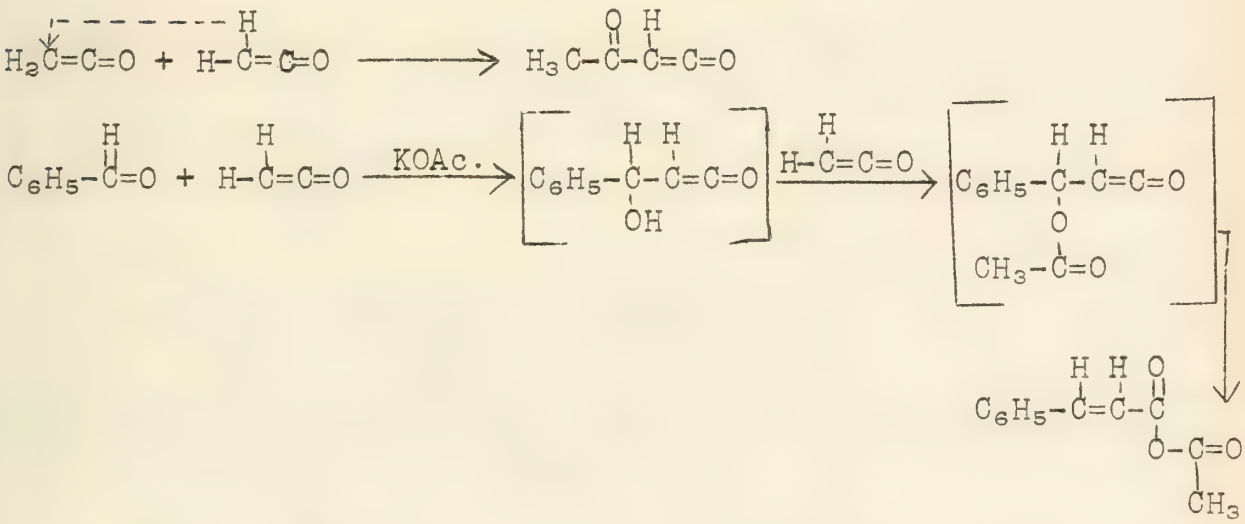


Interesting side reactions take place in this method.



Reactions of Ketones.--

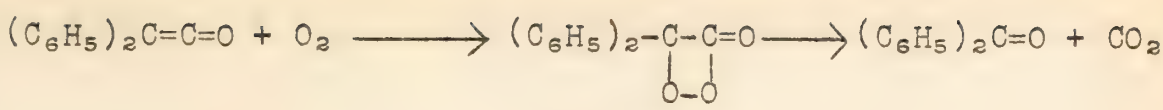
Type 1. Involving the hydrogen atom:

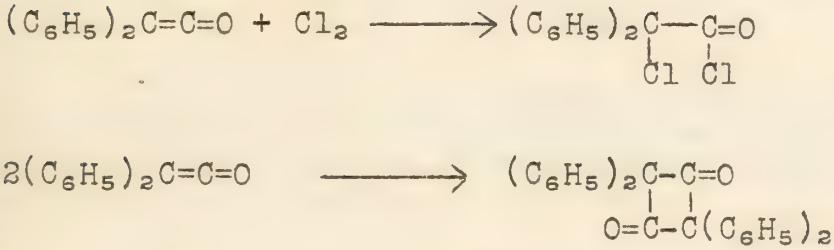


Furfural behaves similarly to benzaldehyde, whereas aliphatic aldehydes and ketones (acetone, acetophenone) do not react.

Type 2. Involving the -C=C- linkage:

The addition of oxygen and of halogen and the polymerization of disubstituted ketones may be formulated as addition to the ethylenic linkage:

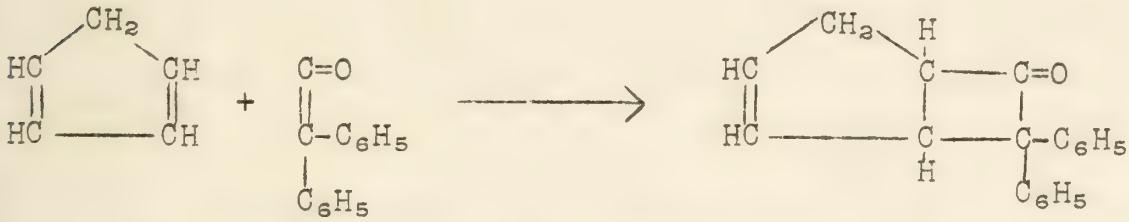




Lipp et al. in an attempt to prepare cyclopropanone obtained cyclobutanone as the chief product when he made ketene react with diazomethane:

Presumably cyclopropanone was an intermediate.

Another interesting addition reaction was reported by L. I. Smith who obtained a crystalline addition compound from diphenylketene and cyclopentadiene.

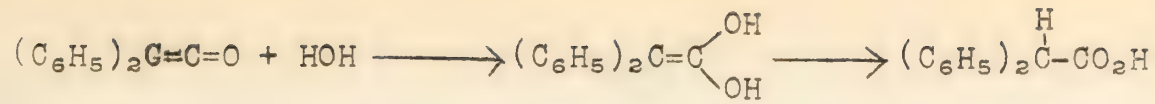


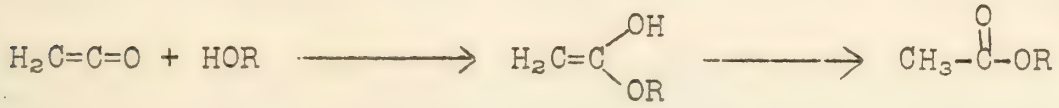
Type 3. Involving the carbonyl:

From a preparative view these are the most useful reactions which ketenes undergo. When ketene reacts with PCl_5, α-chloroacetyl chloride is formed:

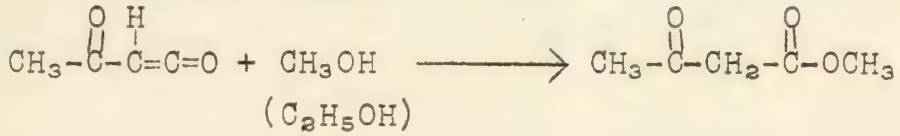
This reaction is significant in that the carbonyl group is shown to be inert to the reagent.

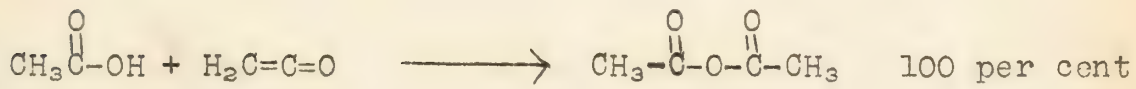
The addition of water, ammonia, amines and halogen acids, that is, HA reagents, is formulated as addition to the carbonyl group followed by ketonization:





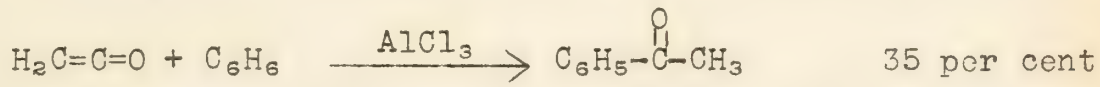
Ketene itself has found an important use as an acetylating reagent. Phenols, mercaptans and alcohols react with ketene to give almost quantitative yields of the corresponding esters. Interesting industrial applications are the following:





Both aliphatic and aromatic acids react to form mixed anhydrides which are useful in the synthesis of mixed esters of cellulose.

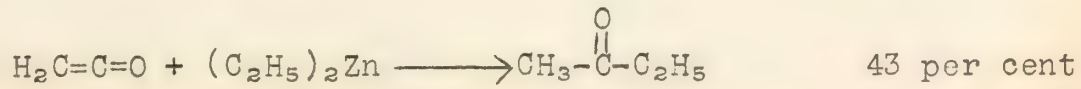
Attempts have been made to use ketene in the Fridel-Crafts reaction:



One and one-half moles of $AlCl_3$ are used per mole of hydrocarbon.

Hurd and his students have attempted the acetylation of sugars with ketene, but obtained oils which were proven by analysis to be partially acetylated products. Thus, in the acetylation of α-methyl glucoside he obtained 3.92 acetyl groups per molecule of the sugar. Hurd found that a trace of H_2SO_4 increased the yields in all of the acetylation reactions which were attempted.

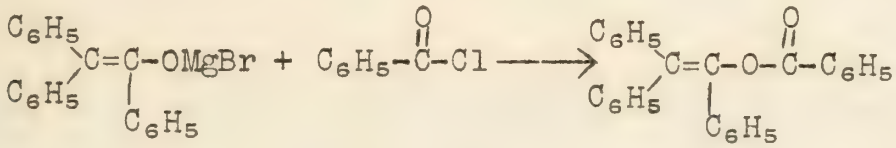
Ketenes react with some of the organometallic compounds and with the Grignard reagent:



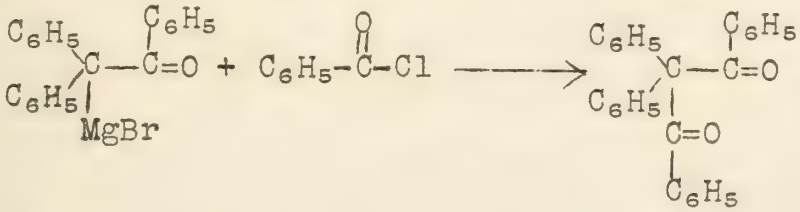
Magnesium diethyl fails to react with ketene. However, mercury dialkyl, allyl mercuric chloride and ethyl magnesium halides do react.

Staudinger in 1907 made diphenylketene react with phenylmagnesium bromide and obtained triphenylvinyl alcohol. He assumed that the Grignard reagent added to the ethylenic linkage, the resulting intermediate then rearranging to the triphenylvinyl alcohol.

Gilman and Hukert in 1920 established the mechanism of the reaction by treating the reaction mixture with benzoyl chloride in order to tag the -MgBr group. Thus, if addition takes place at the carbonyl group, the benzoate of triphenylvinyl alcohol should form:



If, however, addition occurs at the ethylenic linkage, the product should be diphenyl, dibenzoyl methane:



The product actually obtained was the benzoate of triphenylvinyl alcohol, thus proving the addition of the Grignard reagent to the carbonyl group.

Type 4. Involving the oxygen:

There are a number of peculiar reactions reported in the literature involving the oxygen atom of the ketene molecule. A very interesting one is:

$$(C_6H_5)_2C{=}C{=}O + (C_6H_5)_3P{\rightarrow}S \longrightarrow (C_6H_5)_2C{=}C{=}S + (C_6H_5)_3P{=}O$$

Apart from the already mentioned aldo- and ketoketenes, numerous other compounds possess the ketene linkage but do not undergo the general reactions shown by ketenes. Among these carbon suboxide is perhaps the most interesting.

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Reported by M. Witte
December 13, 1939

W. Hückel -- Universität und Hochschule Breslau

For many years, various investigators have proposed mechanisms for substitution reactions which would account for the phenomenon of the Walden inversion. As a result of reaction rate studies, different groups of investigators have recently arrived at mechanisms which explain and also go a long way toward predicting the occurrence of the Walden inversion. The proposed mechanisms, although differing in viewpoint, all yield the same qualitative results.

Perhaps the most extensive work has been done by Ingold, Hughes, and coworkers who propose the following possible mechanisms for nucleophilic substitution reactions:

1. $$R{-}X \longrightarrow R^+ + X^-$$
$$R^+ + Y^- \longrightarrow R{-}Y \qquad (S_N1)$$

2. $$Y + R{-}X \longrightarrow Y{-}R + X \qquad (S_N2)$$

The first type reaction is monomolecular since the first step is the rate determining step. This type reaction may result in a racemic product or a configurationally unchanged product. The second type is bimolecular and always leads to inversion. On the basis of these mechanisms, some generalizations can be made as to whether a substitution would or would not cause a Walden inversion, but many of the effects of varying the reagent or the reaction conditions were left unexplained.

Toward a further study of the Walden inversion, Hückel embarked upon the investigation of substitution on one asymmetric carbon of a compound containing more than one asymmetric center. Since the possible products of such a reaction are diastereoisomers rather than optical antipodes, he believed that the correlation of the structure of the products with that of the starting materials would be simplified.

To this end, he investigated the reaction of various cyclic amines of the hydroaromatic series with nitrous acid to yield an alcohol. The alcohols obtained were indiscriminately the result of Walden inversion, no inversion, or of both simultaneously. In some cases, an unsaturated hydrocarbon, corresponding to that obtained by dehydration of the alcohol, was also obtained. The mechanism proposed was:

$$RNH_2 + HONO + H^+ \longrightarrow [RNH_2]^+ + H_2O$$
$$[RN_2]^+ \longrightarrow R^+ + N_2$$

$$R^+ \xrightarrow{OH^-} ROH$$
$$R^+ \longrightarrow \text{olefine} + H^+$$

This mechanism is of the S_N2 type. On this basis, the only explanation for the fact that in certain cases almost complete inversion was obtained is that steric hindrance in these complicated molecules made substitution without inversion difficult.

Abandoning the amine-nitrous acid technic, Hückel turned to the study of ester exchanges involving the action of potassium acetate on the p-toluenesulfonic esters of cyclic alcohols. The ester exchange resulted in inversion in agreement with the work of Kenyon and Phillips. However, the larger portion of the reaction products consisted of the unsaturated hydrocarbon corresponding to the dehydrated optically active alcohol and of the ether corresponding to the optically active alcohol and the solvent, ethanol. This led to the study of the reaction of the sulfonic esters with ethanol. The reaction was carried out with and without calcium carbonate, the function of which was to neutralize the sulfonic acid formed by the reaction. The products in each case consisted of the unsaturated hydrocarbon and a mixture of the ethyl ethers of the original alcohol and of the inverted alcohol.

The production of the inverted product as well as the unsaturated hydrocarbon can easily be explained by an S_N2 substitution as in the case of the ester exchange. Before this mechanism can be allotted to this reaction, however, it remains to be proven whether or not the uninverted product results from a concurrent reaction in which the sulfonic ester is cleaved thusly: $R\text{-}O\text{-}SO_2C_7H_7$, or whether the ester is cleaved at the R-O bond. If the latter is true, one cannot postulate purely an S_N2 mechanism since this type leads only to inversion. Hückel is now studying the reaction of l-menthyl halides with alcoholates, in which the point of cleavage cannot be doubted, in an effort to clear up this point.

The preparation of l-menthyl chloride was attempted by the reaction of phosphorus pentachloride with l-menthol. Although phosphorus pentachloride has been classified as a reagent which causes inversion, it was found that in one experiment a weakly levorotatory product was obtained, and in another, a strongly levo product. Using very pure phorphorus pentachloride, the product was consistently very weakly levo.

The reagent grade phosphorus pentachloride gave a test for iron, and so a number of reactions were carried out using pure phosphorus pentachloride with the addition of either ferric chloride or aluminum chloride. The chloride obtained was always strongly levo. A maximum levorotation was obtained when an equimolar mixture of the reagents was used. This product was l-menthyl chloride. It was found also that treatment of a mixture of l-menthyl chloride and d-neomenthyl chloride with aluminum chloride or ferric chloride failed to change the rotation of the mixture. Hence, it was deduced that ferric chloride and aluminum chloride effected the steric course of the reaction such that Walden inversion did not take place.

The reverse effect was observed when pyridine was added to the reaction mixture of pure phosphorus pentachloride and l-menthol. The optimum inversion was obtained when the ratio of $1PCl_5:4C_5H_5N$

was used; the product being d-neomenthyl chloride. The yield of the chloride was exceedingly low, most of the alcohol going to form the orthophosphoric ester of the uninverted alcohol.

Phosphorus pentachloride can react as a molecule, as $PCl_3 + Cl_2$, or as $(PCl_4)^+Cl^-$. The presence of complex-forming reagents greatly favors the ionic forms:

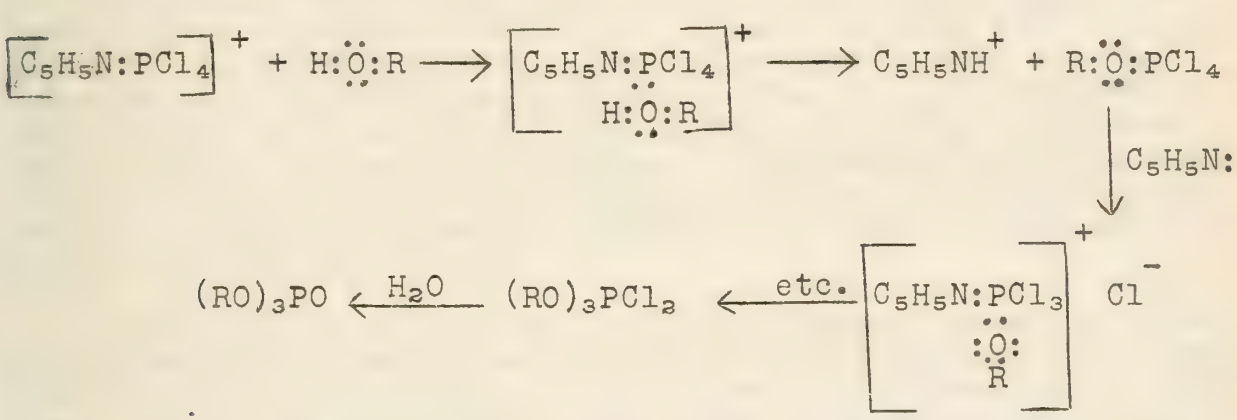
$$PCl_5 + FeCl_3 \longrightarrow (PCl_4)^+(FeCl_4)^-$$

$$PCl_5 + C_5H_5N \longrightarrow (C_5H_5N{:}PCl_4)^+Cl^-$$

$$PCl_5 + 2C_5H_5N \longrightarrow \left[(C_5H_5N{:})_2PCl_4\right]^+Cl^-$$

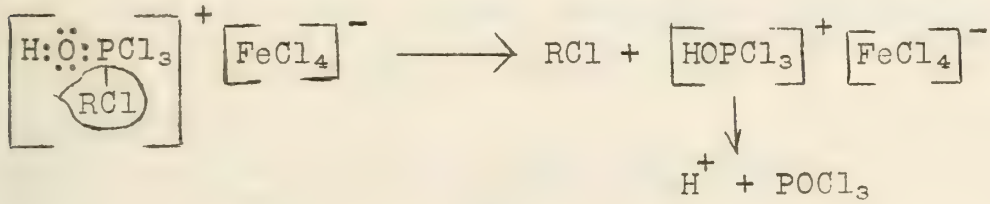
The reaction mechanisms are as follows:

Reaction with pyridine:



This mechanism accounts for the formation of the major product. The formation of the d-neomenthyl chloride results from an S_N2 substitution involving the alcohol and the chloride ion.

Reaction with ferric chloride or aluminum chloride:



Since this is a mechanism of the S_N1 type, the fact that the reaction proceeds entirely without inversion needs to be justified. Comparison of this reaction with the results of similar reactions upon d-octanol-2 furnishes the clue:

d-octanol-2 + PCl_5 $\longrightarrow$ 1,2-chloroctane $\alpha_D = -33.8^\circ$

d-octanol-2 + PCl_5 + C_5H_5N $\longrightarrow$ 1,2-chloroctane $\alpha_D = -34.86$

d-octanol-2 + PCl_5 + $ZnCl_2$ $\longrightarrow$ 70 % 1,2-chloroctane, 30 % d-2-chloroctane $\alpha_D = -15.04$

Notice that in these latter cases the reactions with phosphorus pentachloride and with phosphorus pentachloride and pyridine practically complete inversion took place. The zinc chloride, which can act in a manner similar to aluminum chloride and ferric chloride, exerted a racemizing effect in accordance with the results of an S_N2 reaction. The factor, then, which intercedes in favor of noninversion in the case of l-menthol is probably that of steric hindrance. A consideration of the configuration of l-menthol (1^c-menthyl-3^c-hydroxy-4^t-isopropylcyclohexane) will show that the isopropyl group exerts a shielding effect from the rearward approach of the substituting ion. Thus, the reaction proceeds preferentially toward the noninverted chloride.

Bartlett has studied the replacement of groups at the bridge head of apocamphane. Such a substitution cannot proceed with inversion unless a rearrangement at the bridge head takes place and there is evidence that such rearrangements proceed only through a Walden inversion. The amide of l-apocamphanecarboxylic acid, by the Hofmann hypobromite reaction, yielded l-apocamphylcarbamate which was hydrolyzed to the amine. Nitrous acid converted the amine to apocamphanol-l. The amine reacted with nitrosyl chloride to give l-chloroapocamphane. The alcohol failed to yield the chloride upon treatment with thionyl chloride, phosphorus pentachloride, or hydrogen bromide. l-Apocamphyl p-toluenesulfonate failed to react with lithium chloride. The chloride was stable to alcoholic potassium hydroxide, silver nitrate, and failed to form a Grignard reagent.

These results show that the Hofmann rearrangement of an amide, or the reaction of an amine with nitrous acid or nitrosyl chloride does not involve inversion. The failure of dehydration or elimination of hydrogen chloride to take place is explained by Bredt's rule. The unreactivity of the alcohol and of the chloride can be accounted for in either of two ways:

1. According to Olson, inversion is a prerequisite to substitution. Consideration of this viewpoint uncovers some objectionable features.

2. To adopt Hughes' and Ingold's mechanism, which fits the reaction more logically, one must assume a planar configuration for the intermediate carbonium ion.

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Reported by Alfred A. Albert
January 3, 1940

POLYNUCLEAR CONDENSED SYSTEMS

WITH HETEROCYCLIC RINGS

Borsche -- University of Frankfurt

Borsche and coworkers have conducted numerous experiments on the cyclization of Pr-aryl-quinoline-Pr, carboxylic acids and related substances by intramolecular Friedel-Craft reactions. Their results have been published in a series of six papers from 1937 to 1939.

There are three general preparations for quinoline derivatives:

1. Döbner von Miller synthesis in which an aromatic amine is heated with 2 moles of an aldehyde and concentrated acid.

2. Skroup's synthesis in which an aromatic amine with its o-position free is heated with glycerol and sulfuric acid.

3. P. Friedländer's synthesis consists of the condensation of ortho-aminobenzaldehyde with aldehydes or ketones which contain a $-CH_2$ group adjacent to the -CO group.

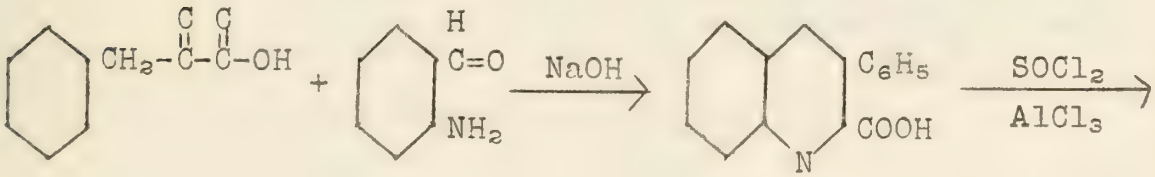
The reactions included in this paper are modifications of reactions 1 and 3.

The pyridine substitution products are examples of the Hantzsch reaction in which 2 moles of β-ketonic acid ester, 1 mole of an aldehyde, and 1 mole of ammonia condense to give the desired product.

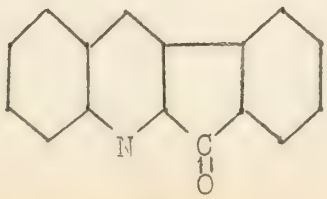
The pyrazoles can be prepared by reacting hydrazine or its derivatives with 1,3-dicarbonyl compounds, or with α,β-unsaturated aldehydes, ketones or acids. Diazomethane or diazoacetic ester also add to acetylenic compounds giving pyrazoles.

A. Benzoazofluorenones and benzoazanthranols.

1. 2,3-Benzo-1-aza-9-oxofluorene (II)

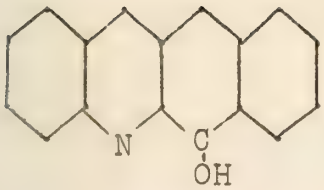


I

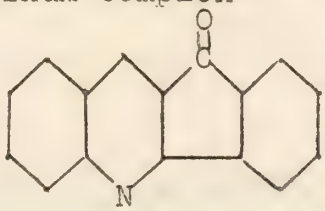


II

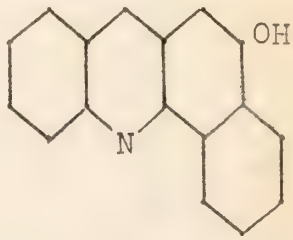
(a) By substituting benzylpyruvic acid for phenylpyruvic acid in above synthesis 2,3-benzo-1-azanthran-9-ol (III) is formed. III was isolated as the aluminum complex.



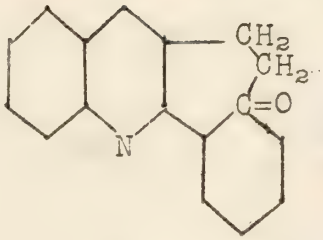
III



IV



V



VI

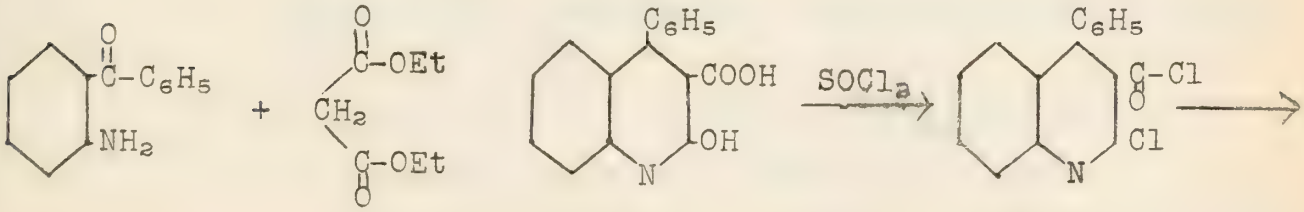
2. 2,3-Benzo-4-aza-9-oxofluorene (IV)

Benzoylacetic acid ester and o-aminobenzaldehyde gives in the presence of NaOH 2-phenylquinoline-3-carboxylic acid whose chloride is converted by $AlCl_3$ in nitrobenzene to IV.

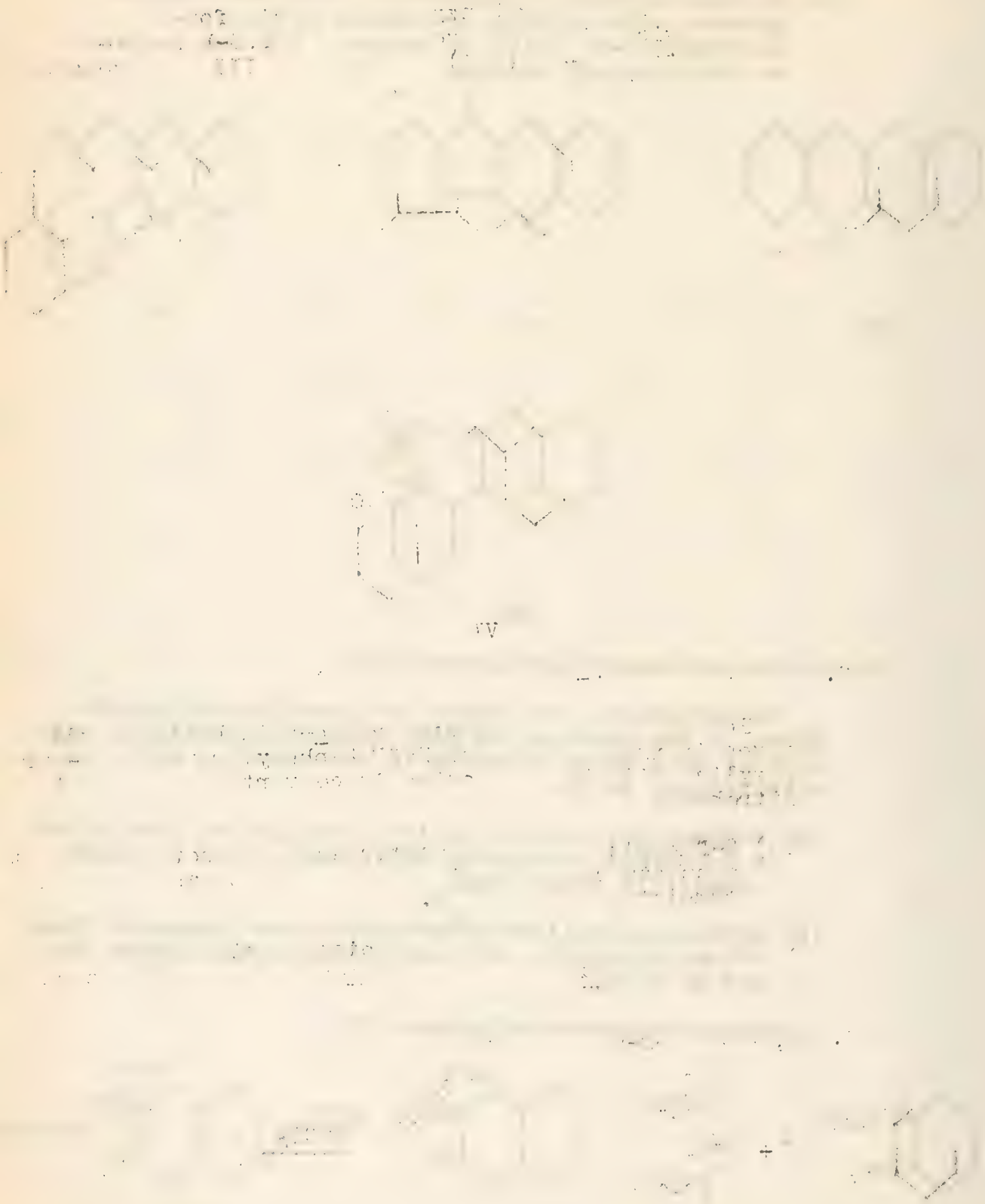
(a) 2-Phenylquinoline-3-acetic acid did not give V but a substance containing sulfur which has not been completely identified.

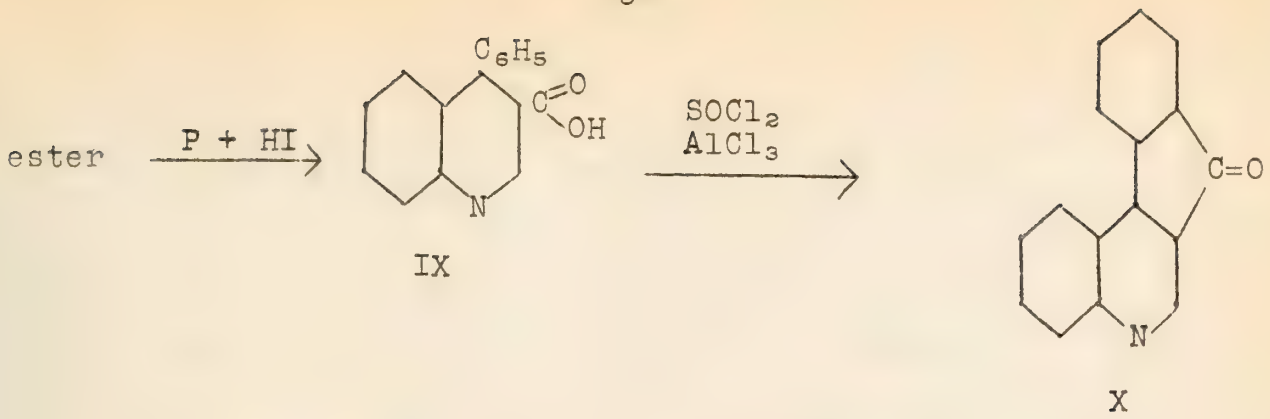
(b) 2-Phenylquinoline-3-β-propionic acid prepared from γ-benzoylbutyric acid and o-aminobenzaldehyde did not give VI.

3. 3,4-Benzo-2-aza-9-oxofluorene (X)

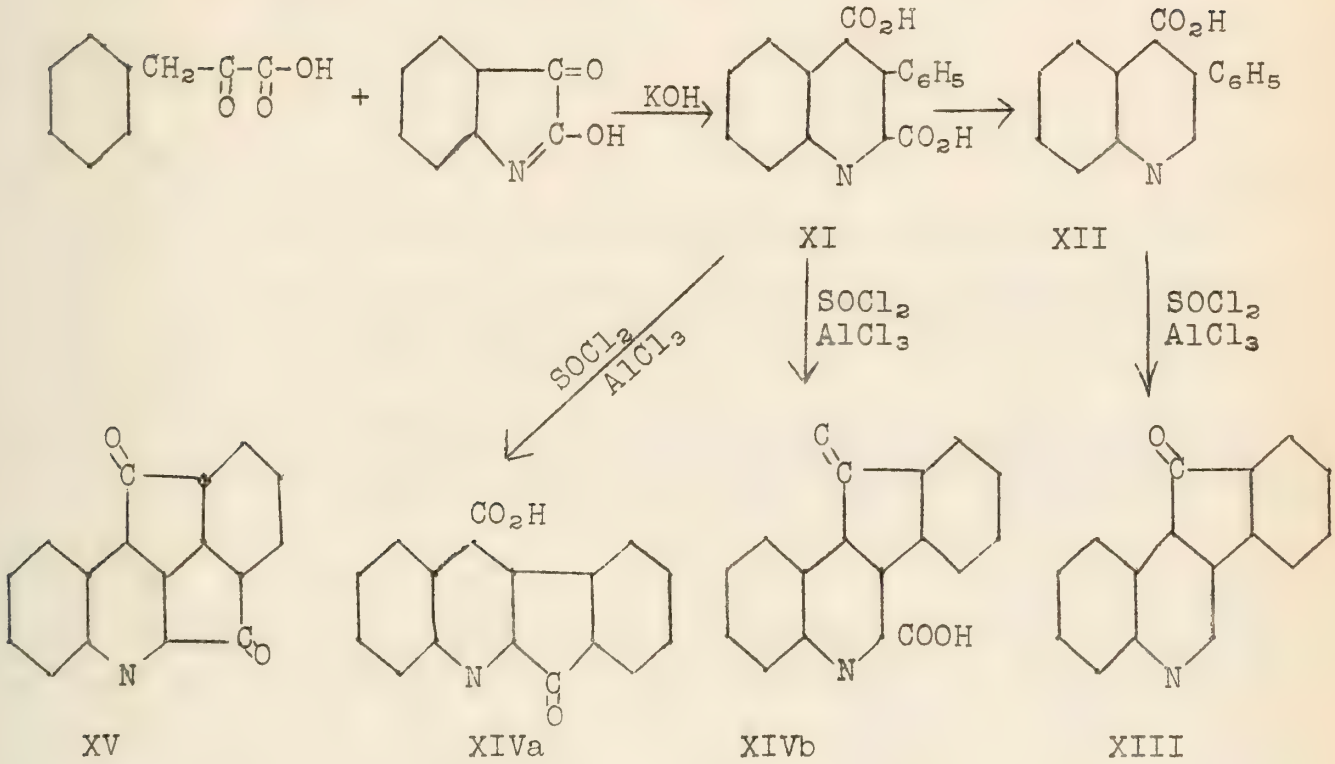


VII VIII





4. 1,2-Benzo-3-aza-9-oxofluorene (XIII)



None of XV was isolated from the Friedel-Craft reaction of XI.

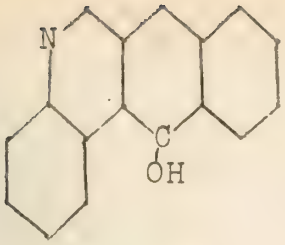
(a) If phenylpyruvic acid is replaced by benzylpyruvic acid in above synthesis 1,2-benzo-3-azanthran-9-ol (XVI) is formed.

(b) From ω-benzyl acetophenone 4-phenyl-1,2-benzo-3-azanthranol is formed.

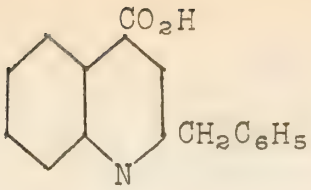
(c) Some 4-substituted 1,2-benzo-3-aza-9-oxofluorenes

(1) 4-Methyl-1,2-benzo-3-aza-9-oxofluorenes.

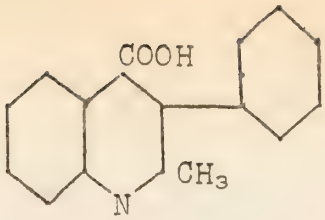
From isatinic acid and phenylacetone two isomers (XVII and XVIII) are obtained dependent on whether the carbonyl attacks the methyl or the methylene group. They can be separated by their solubility in alcohol. XVIII is easily cyclized.



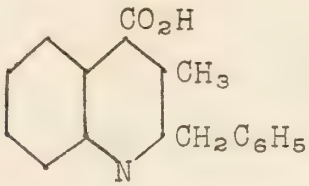
XVI



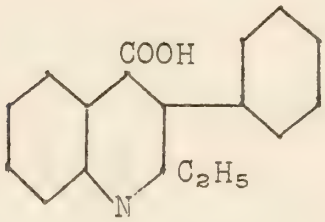
XVII



XVIII



XIX

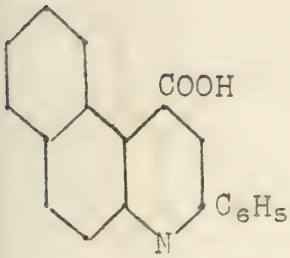


XX

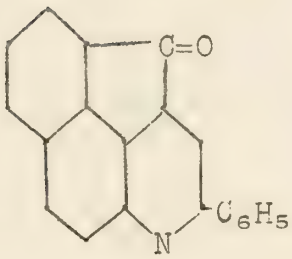
(2) Similarly ethylbenzylketone gives XIX and XX.

(3) With dibenzylketone the 2-benzyl-3-phenylcinchonic acid formed readily but cyclized only with $POCl_3$ + PCl_5.

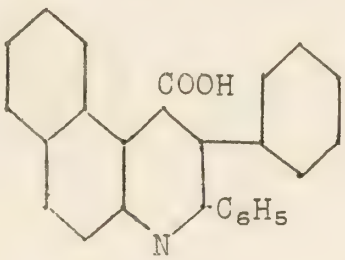
(4) 2-Phenyl-5,6-benzocinchonic acid (XXI) could not be converted to 1-aza-2-phenylphenanthrylene-4,5-ketone (XXII), but XXIII can be converted to XXIV.



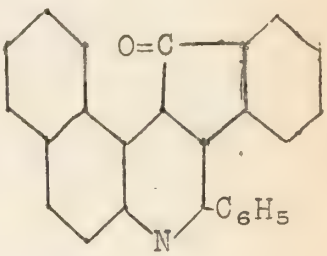
XXI



XXII



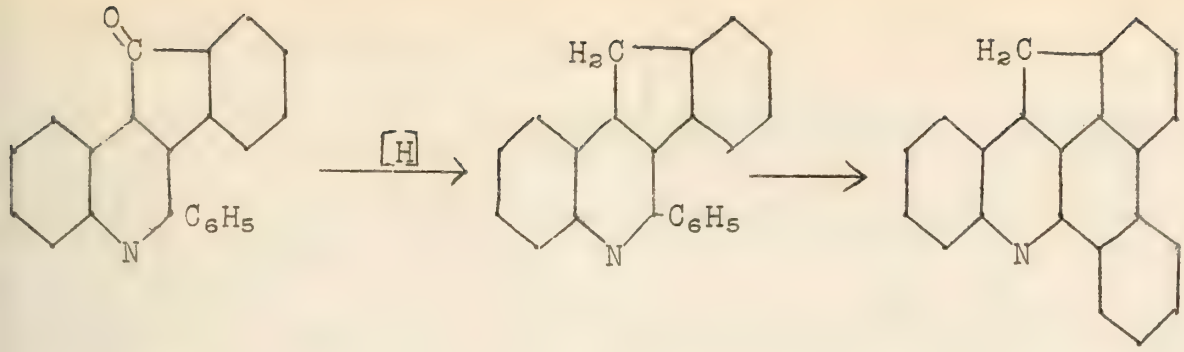
XXIII



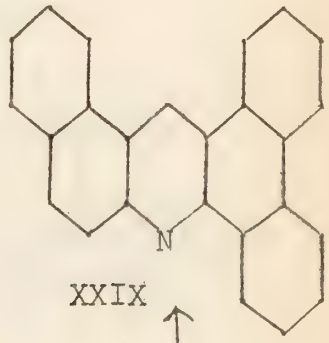
XXIV

XXIII is obtained from β-naphthylamine, phenylpyruvic acid and benzaldehyde.

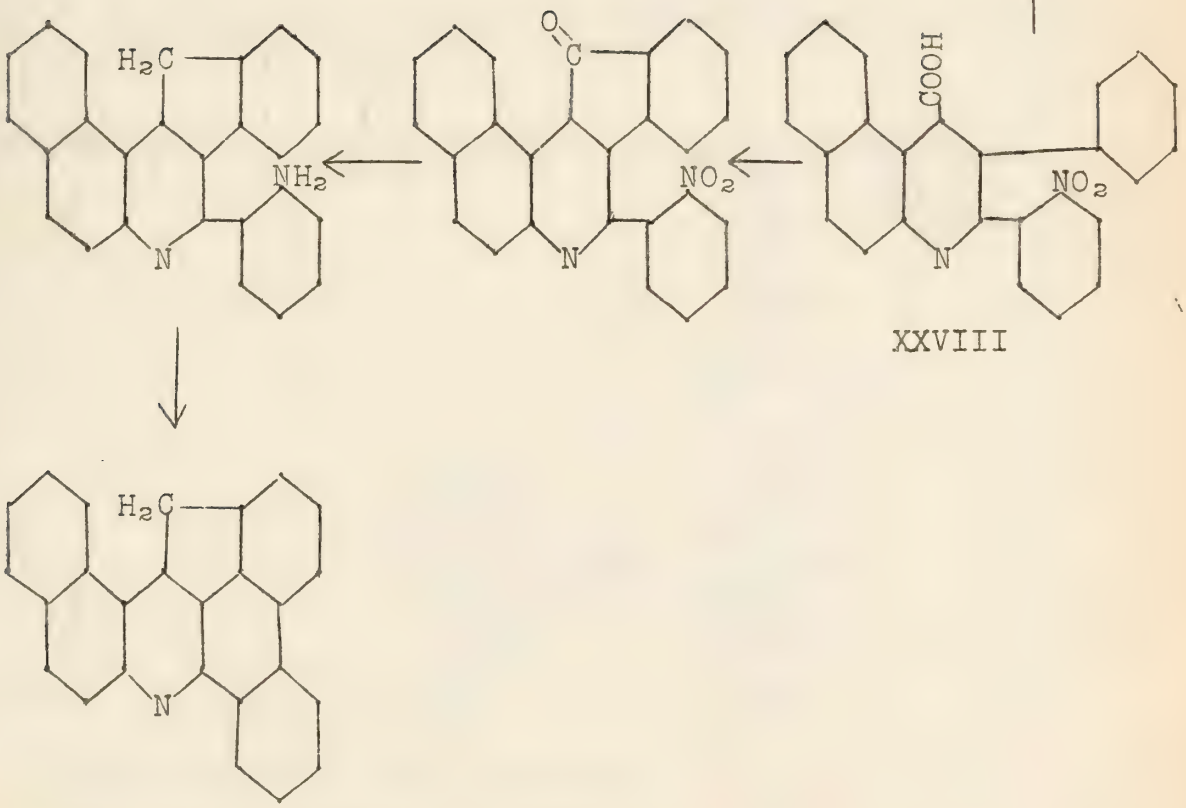
(5) Desoxybenzoin and isatinic acid, followed by cyclization gave XXV which is easily converted to XXVI by hydrazine hydrate. XXVI, however, could not be converted to XXVII with $AlCl_3$. Borsche tried to show that such a ring structure is possible. From β-naphthylamine, phenylpyruvic acid and o-nitrobenzaldehyde XXVIII was obtained. This was converted into XXIX by reduction and decarboxylation followed by diazotization. Borsche tried to obtain XXX by the same process but the last step failed.



XXV XXVI XXVII

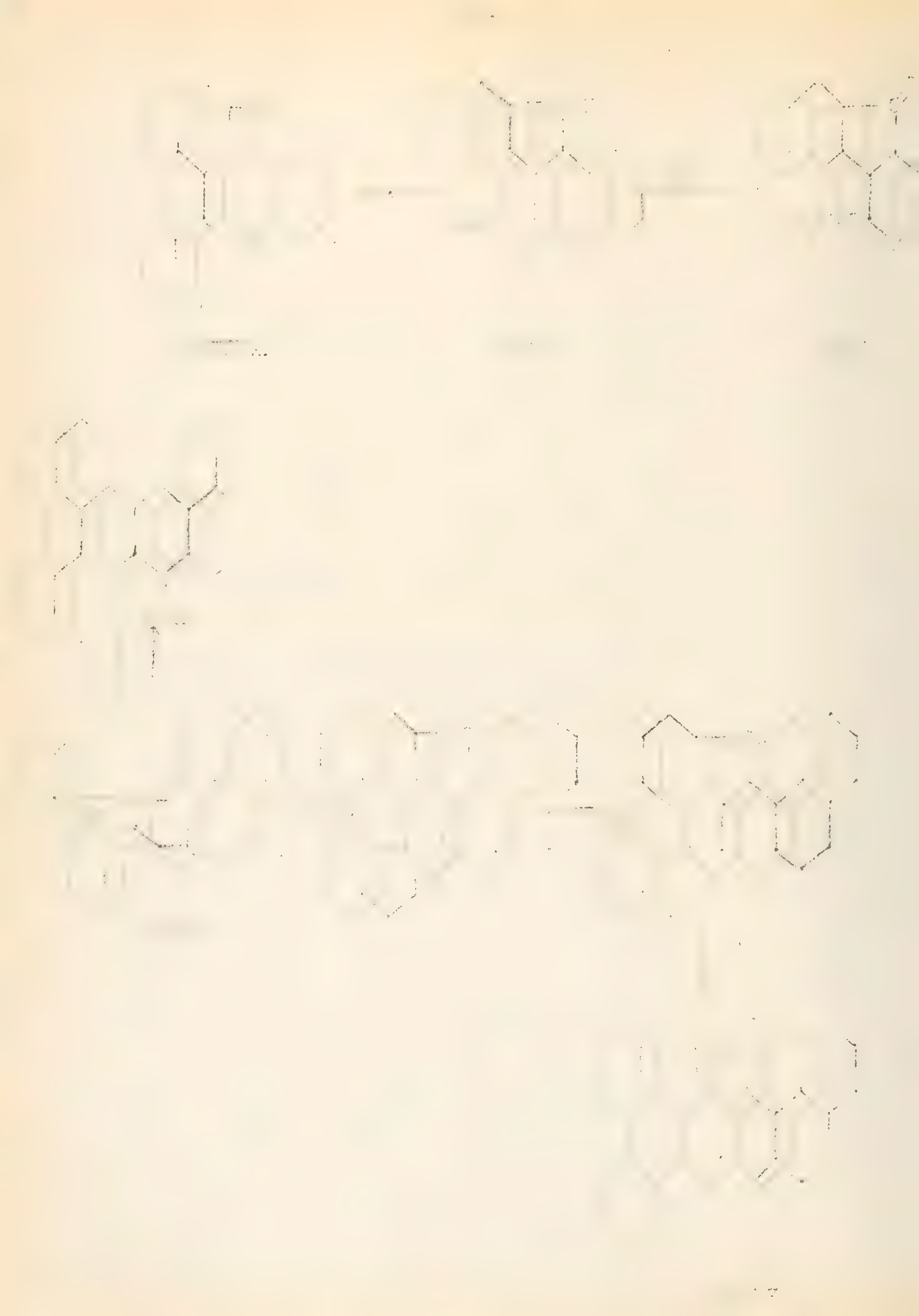


XXIX



XXVIII

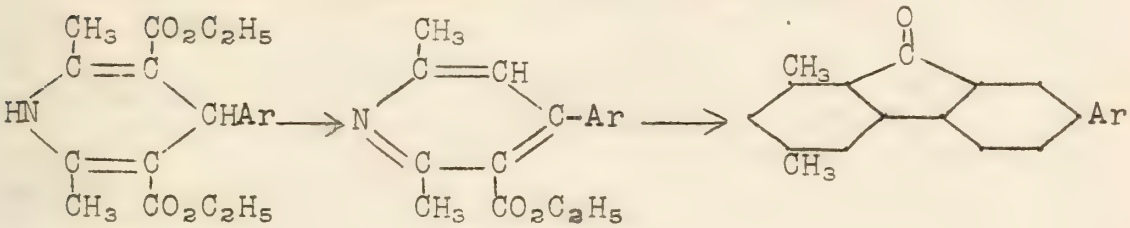
XXX



B. Derivatives of pyridine.

Only when one of the hydrogens of the pyridine nucleus is not substituted does ring closure take place.

1. 1,3-Dimethyl-2-azafluorenones (XXXIII)

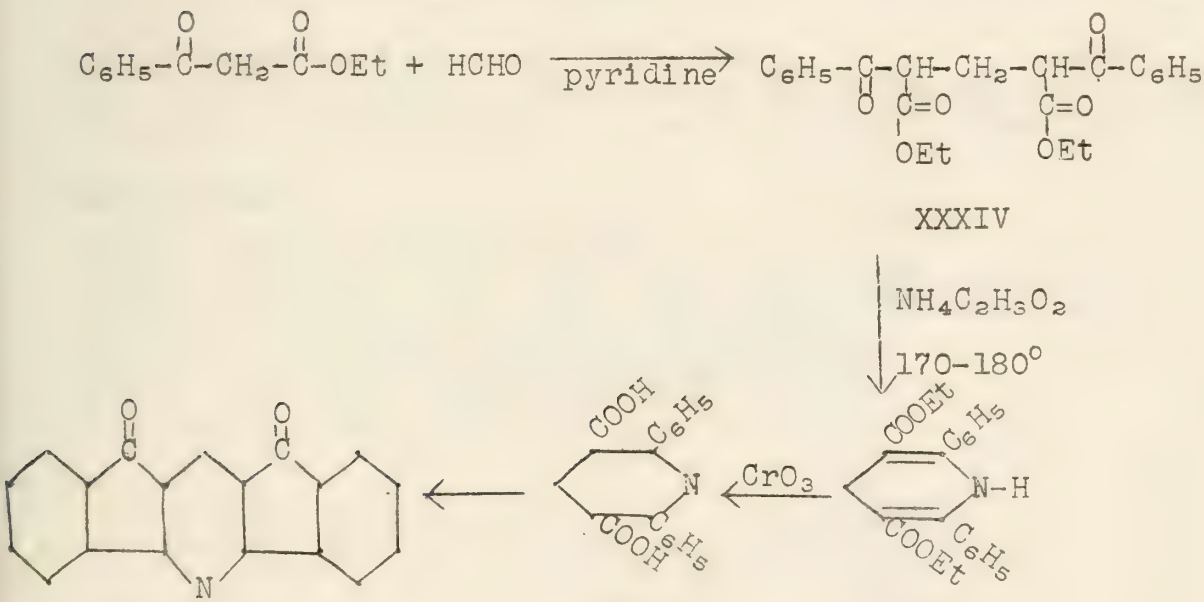


XXXI XXXII XXXIII

Ar = $-C_6H_5$; $-C_6H_5OCH_3$; $-CH_2C_6H_5$; $-C_6H_3$(O)$_2$CH$_2$; $C_6H_5CH{=}CH_2-$

These were all made with acetoacetic ester, β-aminocrotonic acid ethyl ester and the corresponding aryl aldehyde. Only when Ar = $-C_6H_5$; $-C_6H_5OCH_3$; and $-C_6H_3$(O)$_2$CH$_2$ were the yields good.

2. 2,3,5,6-Dibenzoylpyridine (XXXVII) was prepared by the following synthesis.



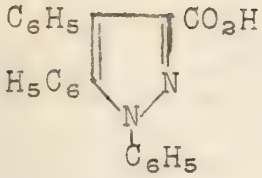
XXXIV

XXXVII XXXVI XXXV

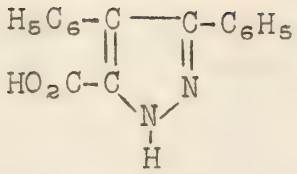
C. Pyrazoles and 1,2,3-triazoles.

No ring closures took place.

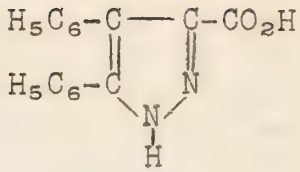
1.



XXXVIII

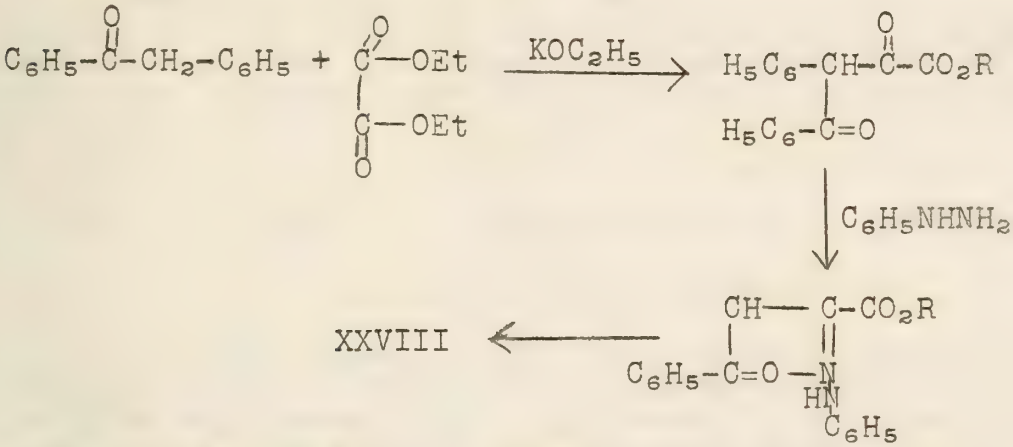


XXXIX



XLII

Synthetis of XXXVIII:



XXXIX and XL are isomers obtained from desylglyoxylic acid ethyl ester and hydrazine. The inability to form rings was not due to inactivity of $-\overset{O}{\overset{\|}{C}}-Cl$ because benzene would condense with these substances easily. Derivatives of 1,2,3-triazols also did not give ring closure.

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Reported by James Harkema
January 3, 1940

MOLECULAR CONSTITUTION AND BOILING POINTS

V. C. E. Burnop -- Imperial College, London
C. R. Kinney -- University of Utah

The earliest attempt to relate the boiling point with the chemical constitution of organic compounds was Kopp's theory in 1842 that equal differences in composition produce equal differences in boiling point, in particular, that the difference in boiling point between successive members of an homologous series is always 19°. The attempts since that time to formulate a relationship have until recently concentrated on obtaining some empirical equation relating molecular weight or number of carbon atoms with boiling points of homologous series of nonassociated liquids.

Burnop has attacked the problem from a different angle. He has defined the empirical function $b = M \log T + 8.0\sqrt{M}$, and has demonstrated that for nonassociated liquids it is an additive function. His various atomic and structural values are as follows:

C = 23.2 H = 10.9 F = 68 Cl = 121.0 O = 51.0 N = 39.7

Br = 255 I = 398 double bond = 16.1 triple bond = 33.0

six-membered ring = 17.6

For normal paraffins the check between the calculated and observed values is very good, except for methane. Unfortunately, his formula does not allow for branched-chain compounds. Table I gives a few of his results on the hydrocarbons.

Table I

	b(obs.)	b(calc.)
methane	64.8	66.8
ethane	112.0	111.9
propane	156.9	156.9
n-butane	202.3	201.9
n-pentane	247.3	247.0
2-methyl butane	246.4	247.0
tetramethyl methane	244.6	247.0
n-hexane	292.1	292.0
n-heptane	337.3	337.0
n-octane	382.1	382.0
n-nonane	427.1	427.1
ndecane	472.0	472.1

The discrepancy in the case of the three isomeric pentanes is greater than it would seem from the figures, since the small differences in b produce large differences in the boiling point. The boiling points of the three compounds are respectively 309°A, 301°A, and 283°A.

Olefins again check well, except when there are two or more double bonds in the molecule, in which case the contribution of the bonds depends on the number of carbon atoms separating them.

It is perhaps worthy of note that molecules containing conjugated systems are not anomalous.

Burnop has tabulated the observed and calculated values of b for cycloparaffins, halides, ethers, esters, amines, and ketones, with fair agreement in all cases except the aliphatic ketones, where the observed values are consistently about three units lower than the calculated values.

Perhaps the most unexpected success of Burnop's function is in the aromatic series. Considering benzene as cyclohexatriene, he calculates a value of 270.5 for b. The observed value is 269.6. This close check holds good for all aromatic compounds cited except anthracene. Unfortunately, Burnop has included no derivatives of the aromatic hydrocarbons.

Burnop's function can be used as such only for nonassociated liquids. In a later paper he has attempted to calculate degree of association from a comparison of the actual with the calculated value of the boiling point. His values are in only fair agreement with those of Ramsay and Shields from surface tension measurements. The validity of this use of the function is questionable.

Kinney has proposed another, quite different, additive function of the boiling point: the boiling point number, or b.p.n., defined by the following equation, $\log bpn = 3\,[\log(t + 543) - 2.3620]$, where t is the centigrade boiling point.

Kinney's system takes into account branching in the chain - the longest straight chain in the molecule is taken as the base, each C contributing 0.8, and each H, 1.0, but any branching in the chain is taken care of by considering the molecule as an alkyl derivative, values being assigned to the methyl, ethyl, propyl, and butyl radicals. The system includes both associated and nonassociated compounds, values being given for the following groups: -Cl, -OH, -O-(in ethers), O= (differing in aldehydes and ketones), -COOH, OO (in esters), $-NH_2$, -NH-, =N-, -C≡N, and -N≡C. These values vary according to the position of the group in the molecule, being largest when the group is primary. The agreement between observed and calculated bpn's is striking, deviation being large only for the methane derivatives (as was also the case with Burnop's function) and with certain compounds having two methyl groups attached to the same carbon atom in the chain. No correction was proposed for this since in no case did the deviation exceed five per cent. Table II shows the calculated and observed values for the chloropentanes.

Table II

	Calcd.		Obs.	
	BPN	BP	BP	BPN
1-chloropentane	22.5	106.7	108.35	22.67
2-chloropentane	21.5	96.9	96.7	21.48
3-chloropentane	21.5	96.9	97.3	21.54
1-chlor-2-methyl butane	21.75	99.4	98.3	21.64
2-chlor-2-methyl butane	20.25	84.3	86.0	20.41
3-chlor-2-methyl butane	20.75	89.4	91.0	20.91
4-chlor-2-methyl butane	21.75	99.4	99.6	21.77
1-chlor-2,2-dimethyl propane	21.0	92.0	84.4	20.26

The agreement is good for all of these compounds except the last, which is seen to be one of the above-mentioned 2,2-dimethyl derivatives. Incidentally, this compound showed a larger deviation than any other of its class.

Of all the compounds studied, the alcohols agreed least closely with the calculated values, but even here the mean deviation in the bpn's was less than 1.0. The mean deviation for all compounds studied was about 0.4. In nearly every series studied the largest deviation was found in the compound having ten carbon atoms. No explanation is offered. An exception is tri-n-heptylamine, the reported boiling point of which is 20° below that calculated. Kinney contends that, since it is very high-boiling (reported 330°), and is out of line with the other tertiary amines, its boiling point was probably incorrectly determined. The boiling points of the only other two compounds which were off so much as five per cent were determined at 729 mm. Kinney has not extended his system to include unsaturated and cyclic compounds.

The possible future usefulness of the two functions discussed cannot be foreseen. The parachor and molecular refraction have proved to be very useful tools for the organic chemist. Each is limited in its usefulness, not only by inability to distinguish certain types of isomers, but also by experimental difficulties in the case of the parachor. The parachor is defined by the equation:

$$P = \frac{M\gamma^{\frac{1}{4}}}{D-d}$$

It is useful in distinguishing between double and triple bonds, size of rings, O in alcohols and in ketones, etc. It does not distinguish between straight and branched chains, nor between ortho-, meta-, and para-aromatic derivatives. It is purely additive, taking no account of position of groups. In the case of hydrocarbons, D. T. Lewis has suggested the following relationships between parachor and boiling point:

$$P = \ell^{(T + a)/K}$$

where K is a universal constant, and a is a constant which varies with the degree of unsaturation. Obviously the relationship is only approximate, since it cannot hold for both straight and branched chains.

The molecular refraction, defined by the equation

$$R = \frac{n^2-1}{n^2+2} \cdot \frac{M}{d}$$

is usually easier to determine than is the parachor. Its field of usefulness if very nearly the same except that conjugated double bonds cause a large exaltation. This increases its usefulness in certain fields. It is noteworthy that benzene, pyridine, cyclopentadiene, etc., show no exaltation, but naphthalene, anthracene, etc., do.

It will be noticed that Burnop's function appears to fail in precisely the same cases as do the parachor and molecular refraction. Kinney's function, however, is most strikingly, valid in this field. The boiling point is the most easily obtained property of liquids, and the usefulness of this system seems to be limited only by the number of varieties of compounds to which it can be extended.

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Reported by J. T. Fitzpatrick
January 10, 1940.

THE STRUCTURE OF ELLIPTONE

Stanley H. Harper -- Rothamsted Experimental Station, Harpenden Herts
Th. M. Meyer and D. R. Koolhaas, Laboratorium voor Scheikundig Onderzoek, Buitenzorg (Netherlands Indies)

A large number of species of derris is found in the Eastern tropics and in Mologa. The powdered, dried roots are useful as insecticides. In the last few years there have been extensive investigations of the active components of this root. A short survey of these substances is given by Meyer and Koolhaas.

Rotenone, which is converted to isorotenone (I,R = isopropyl) by treatment with sulfuric acid, was obtained from the ether extract of dried derris root. The residual extract, a "derris resin" contained elliptone.

The toxic effect of elliptone on caterpillars was shown to be comparable to that of rotenone.

Buckley, in 1936, isolated a substance by treating an ethereal solution of the resin with 5 per cent potassium hydroxide, which was optically inactive and from its color reactions appeared to be related to rotenone. Harper obtained Buckley's crystalline compound from the neutral resin by chromatographic adsorption on alumina. From its empirical formula and the similarity of its reactions to rotenone he proposed the structure indicated by formula I, R = H. He later showed this to be correct.

Since Buckley's compound is inactive and the derris resin is active it was believed that some transformation had taken place during the alkali treatment. This precursor, *l*-elliptone, was isolated by Meyer and Koolhaas. It precipitated from the ether extract of the derris root, and was recrystallized from methyl alcohol. Harper showed that by the action of sodium acetate in boiling alcohol this active elliptone racemized completely. Cahn, Phipers and Boam had shown previously that this type of racemization on rotenone-like substances was specific for C_7C_8 isomerism. The dl-elliptone thus obtained was the same as Buckley's compound.

The structure I (R = H) was then advanced for elliptone, based on the following evidence.

1. The analytical data established the formula $C_{20}H_{16}O_6$; and the presence of two methoxyl groups.

2. Positive Durham, Meyer, and Goodhue color tests, specified for structure of the type found in rotenone were obtained.

3. The fact that treatment with sulfuric acid did not cause isomerism or dehyration indicated that R = H.

4. Oxime formation showed the presence of a ketonic group.

5. Iodine in boiling alcoholic sodium acetate gave the inactive dehydro derivative (II). This is further evidence for the C_7C_8 isomerism.

6. A negative ferric chloride test, no iodine derivative in the preparation of the dehydro compound and alkali insolubility indicated the absence of a phenolic group.

7. The formation of an inactive monoacetate by the action of acetic anhydride indicated enolization.

8. Results of oxidative and hydrolytic degradation and catalytic hydrogenation reactions similar to those studied with iso-rotenone, finally proved the structure.

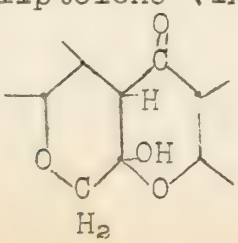
The dehydro derivative (II) formed elliptic acid (III) through hydrolytic fission. III was oxidized to derric acid (IV) with alkaline hydrogen peroxide, or to rissic acid (V) with permanganate. The methyl ester of elliptic acid was formed by the action of diazomethane, but the phenolic ether was not obtained, thus indicating two substitutes ortho to the phenol. Derric acid (IV) was also obtained from a similar series of reactions starting with iso-rotenone. This series of reactions fixes the structure of rings A, B, and C.

In order to determine the exact nature of rings D and E, and the substituent R, the alcoholic alkali cleavage was studied. In the case of iso-rotenone it gave iso-tubaic acid (VII, R = isopropyl). From elliptone by a similar reaction a different monobasic phenolic acid resulted. It was decarboxylated by heating above the melting point. The product is probably 4-hydroxycoumarone-5-carboxylic acid (VII, R = H). This compound was synthesized, and the two proved to be identical. Thus, with the solution of the form of rings D and E, the position of the OH group on D (in VII) and the nature of R, the structure of the whole molecule was established.

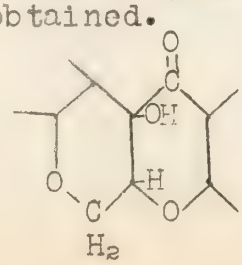
When I was oxidized with chromic acid a substance $C_{20}H_{12}O_7$ was formed. Formula VI was suggested as a possible structure. VI dissolved in 5 per cent aqueous sodium hydroxide, and gave a monophenyl hydrazone. VI is similar to rotenone also obtained by chromic acid oxidation.

The structure represented by formula VIII was suggested for the product of catalytic hydrogenation. However, its probable empirical formula of $C_{20}H_{26}O_5$ does not fit formula VIII.

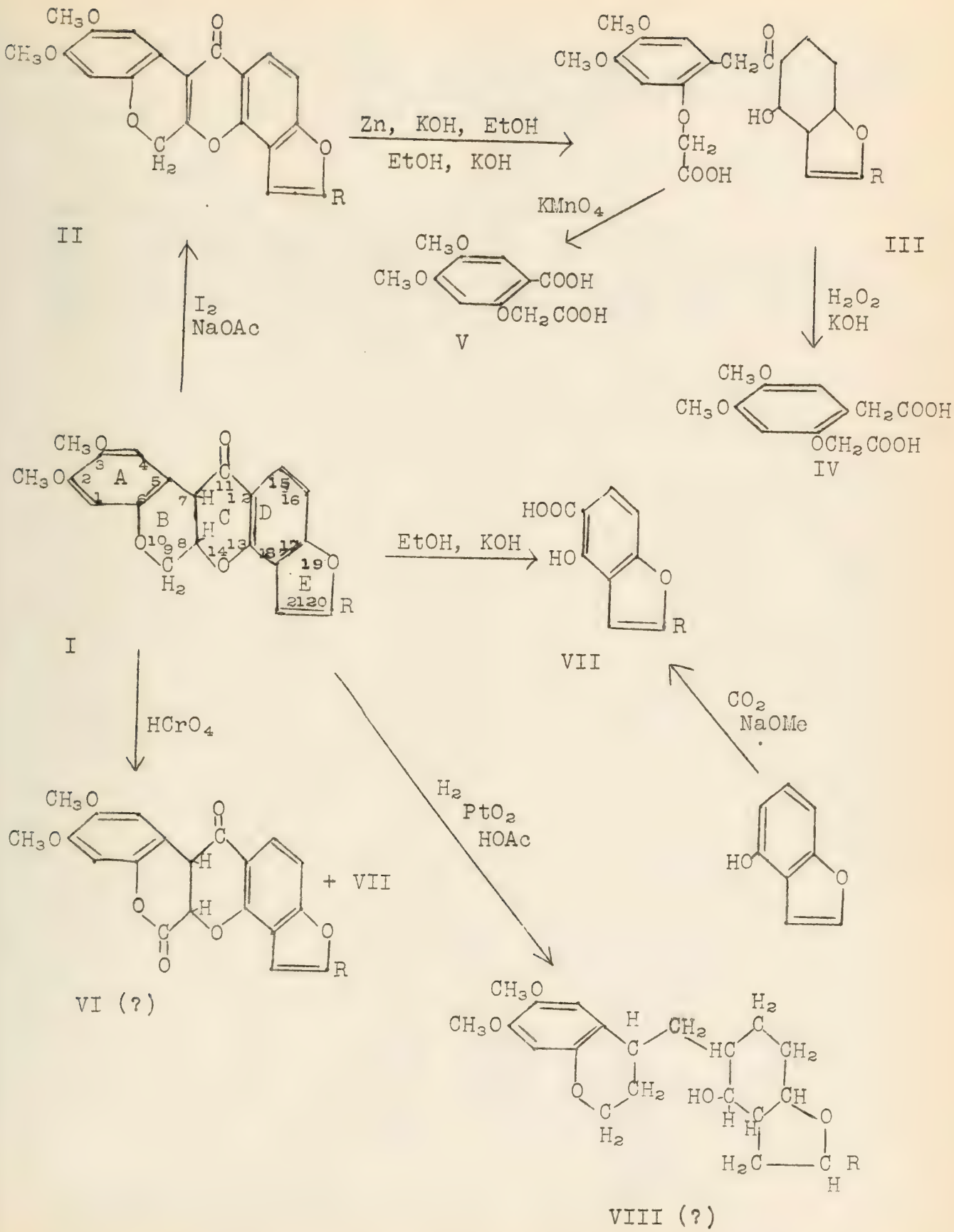
In the iodine-sodium acetate reaction to give II the acetate of elliptolone (IXa or IXb) was also obtained.



IXa



IXb


Zn, KOH, EtOH
EtOH, KOH
KMnO4
H2O2
KOH
I2
NaOAc
EtOH, KOH
HCrO4
H2
PtO2
HOAc
CO2
NaOMe
II
III
IV
V
I
VII
VI (?)
+ VII
VIII (?)

The acetate was dehydrated with alcoholic sulfuric acid to II, and the acetate on heating lost acetic acid to form II directly. This loss of acetic acid on heating explained the apparent dimorphism recorded by Meyer and Koolhaas.

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Reported by C. A. Sperati
January 10, 1940

REARRANGEMENTS OF ALLYL ETHERS

Charles D. Hurd -- Northwestern University
Walter M. Lauer -- University of Minnesota
Otto Mumm -- University of Kiel

The allyl rearrangement is a pyrolytic reaction taking place at about 200-250°C. There are three general rules which the pyrolysis of ethers follow:

1. Aliphatic ethers always tend to form aldehydes or ketones as the principal products of pyrolysis.

2. If one of the groups attached to the oxygen in the ether is aromatic, phenols are formed.

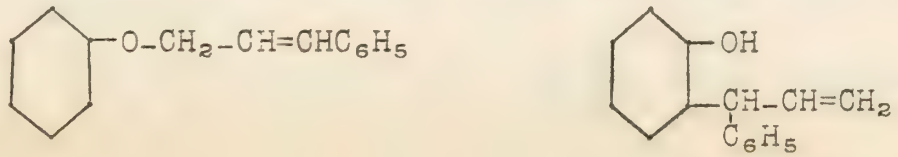
   The difference in the relative electronegativity of the phenyl and the alkyl radicals may cause the difference in the mode of reaction of the two types of ethers (1 and 2).

3. In the case of unsaturated ethers of the type $R\text{-}O\text{-}C{=}C^{*}$, the R group wanders to the β-carbon atom which bears the asterisk.

Phenyl ethers belong to both classes (2) and (3). Again the relative electronegativity of the two groups attached to the oxygen is the deciding factor as to the decomposition which takes place. In anisole and, its homologs, the methyl group is fairly electronegative as compared to the phenyl and is not readily detached from its valence electrons; hence rule (2) is obeyed. In allyl phenyl ether, the allyl group is quite electropositive in comparison to the phenyl group; thus phenyl allyl ether obeys rule (3) and rearranges very smoothly into o-allylphenol:

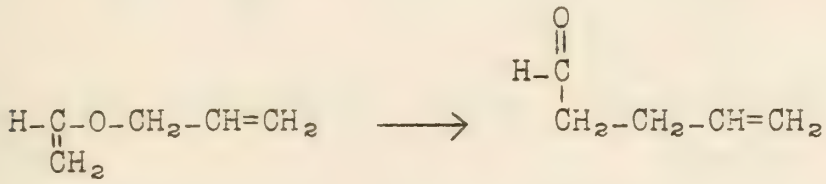
The allyl group almost invariably migrates to the ortho position of the aromatic nucleus, but will go para if both ortho positions are substituted.

The wandering allyl group does not become attached to the ortho-carbon atom of the ring through the same carbon by which it was originally linked to the oxygen. Proof of this fact was first given by Claisen and Tietze by the use of a properly substituted allyl chain. Thus when phenyl cinnamyl ether is heated, the product is not o-cinnamylphenol, but instead is o-(α-phenylallyl)-phenol thus:

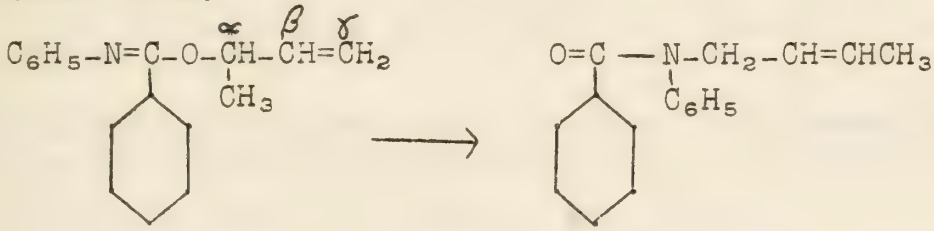


Allyl groups which are substituted in the γ-position or monosubstituted in the α-position behave in this reaction like the allyl group itself. However, an allyl group containing α,α-disubstitution does not rearrange, but splits into a phenol and a diene.

Hurd and Pollack have synthesized and studied the simplest possible allyl ether which has the structural grouping necessary for this rearrangement, vinyl allyl ether, $CH_2{=}CH{-}O{-}CH_2{-}CH{=}CH_2$. The rearrangement of this ether proceeds very regularly following rules (1) and (3) at 255°C. in the vapor phase. It formed only one product as shown in the equation below, and did so in 40-50% yield.

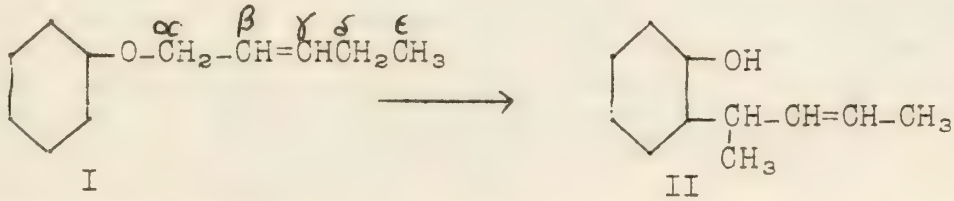


The rearrangement of this ether is not complicated by the simultaneous migration of a hydrogen atom as is the case in the rearrangement of the phenyl allyl ethers. The same is true of the rearrangements studied by Mumm and Moller in which they used allyl imido ethers thus:



In these experiments also it is the γ-carbon atom which becomes attached to the nitrogen during the rearrangement.

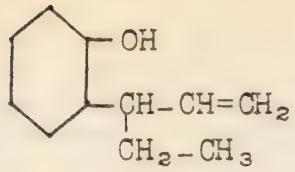
Mumm and Moller also performed experiments on para-allyl rearrangements using a cinnamyl aryl ether in which both ortho positions were blocked. In this case, the product showed that no inversion of the wandering cinnamyl group had taken place. Lauer and Filbert also worked on this question of the inversion of the wandering radical. They found the following rearrangement to take place,



I II

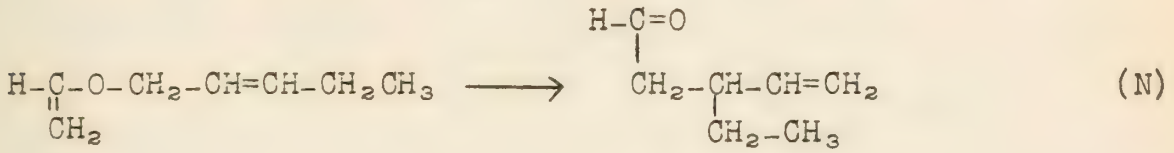
which means that it was not the γ-carbon atom of the substituted allyl group which became attached to the nucleus, but either the β or the δ-carbon atom.

Hurd and Pollack repeated and confirmed this work and showed further that along with 42% of the abnormal product, 56% of the normal rearrangement product (III) was formed.

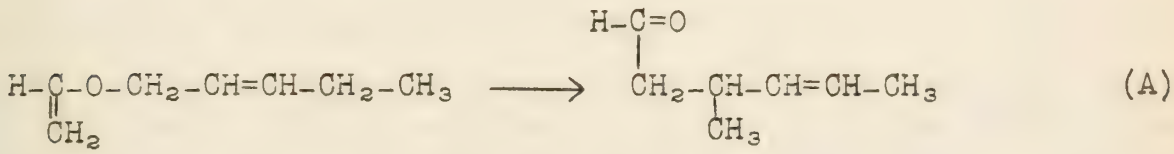


III

Hurd and Pollack then investigated γ-ethylallyl vinyl ether whose normal and abnormal rearrangements would be represented respectively by equations (N) and (A) below:



(N)



(A)

About 76.5% of the normal and 4.6% of the abnormal rearrangement products were formed.

An acceptable mechanism of the allyl rearrangements must be able to explain the following peculiarities:

1. The intramolecular nature of the process.
2. Inversion of the wandering group in <u>ortho</u> rearrangement.
3. The failure of α,α-disubstituted allyl ethers to rearrange, and the formation of a phenol and a diene in such cases.
4. The abnormal rearrangement of γ-ethylallyl phenyl ether.
5. The evolution of propylene from allyl 2,4,6-trialkylphenyl ethers.
6. The fact that all phenyl ethers do not rearrange as does the allyl.

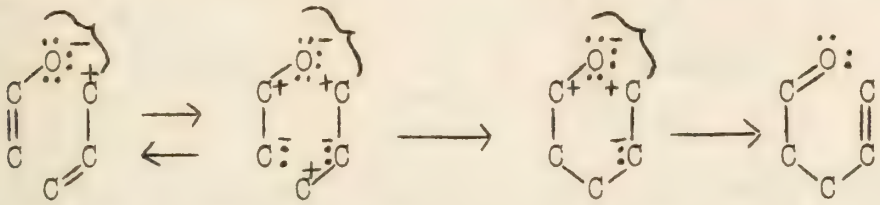
Free radical mechanisms are unsatisfactory because they are not in accord with the observations that (1) the temperature of the reaction is comparatively low, and (2) no peroxides, such as ph-o-o-ph, which this theory would predict as a by-product have ever been found. Moreover both free radicals and ionic mechanisms would give rise to intermolecular changes whereas the reaction is undoubtedly an intramolecular one.

Hurd's and Mumm's mechanisms are essentially the same, but Mumm's is not expressed in terms of electrons, and hence lacks the clarity and simplicity of the former.

Hurd first assumes that "the initial effect of heat on the system C=C-O-C-C=C is to alter the position of the pair of electrons which bind the allyl group to the oxygen so that a semi-

ionization occurs such as C=C-Ö: C-C=C.

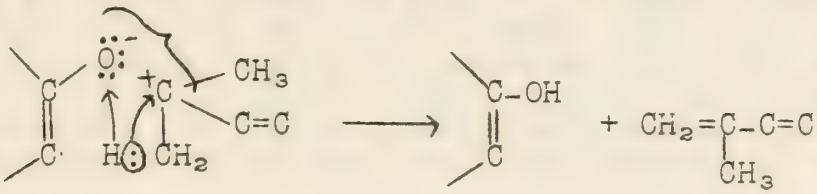
"Actual separation into ions does not occur, but the semi-ionization product promotes other ionic disturbances at the double bonds. This effect, combined with the spatial proximity of the atoms at the end of the systems, brings about the temporary ring closure and readjustment of electrons as shown in the following sequence of steps:"



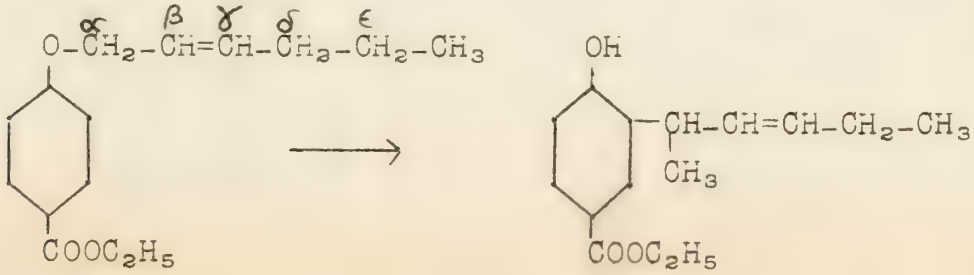
(or its enol form)

This mechanism accounts for peculiarities (1) and (2) listed above.

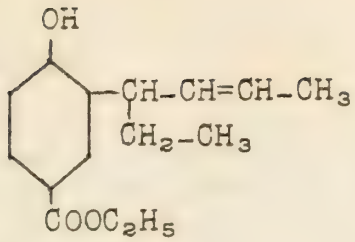
To obtain the spatial proximity of the γ- and the ortho-carbons mentioned above and the consequent cyclization there must be free rotation about the bonds. This condition is met in the simple cases. According to Hurd, however, "if it be assumed that there is a restricted rotation about the carbon to oxygen bond in α,α-dialkyl aryl ethers, then a satisfactory picture for the scission into a phenol and a diene may be constructed. Thus the positive α-carbon of the allyl group may satisfy its electron deficiency not only by appropriating electrons from the neighboring double bond, but also from a neighboring C-H bond, the released proton being attracted to the oxygen." This gives rise to a phenol and a diene as shown below and accounts satisfactorily for our third peculiarity:



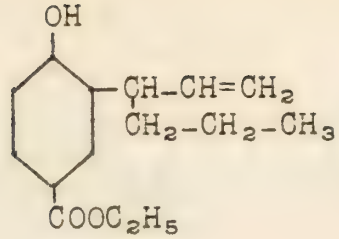
Hurd explained the mechanism of the abnormal rearrangement of (I) by assuming that the δ-carbon atom of its sidechain is the one which becomes attached to the ortho-carbon atom in (II). Lauer has shown, however, that in the case of ethyl p-(γ-propyl-allyloxy)-benzoate (IV), the β-carbon is the one involved in this rearrangement. Only this conclusion can account for the product obtained (V), whereas if a shift to the δ-carbon atom had occurred, it would have produced (VI) as the abnormal rearrangement product.



IV V



VI



VII

Actually no (VI) was obtained, but (VII), the normal rearrangement product, was also produced in the reaction along with (V).

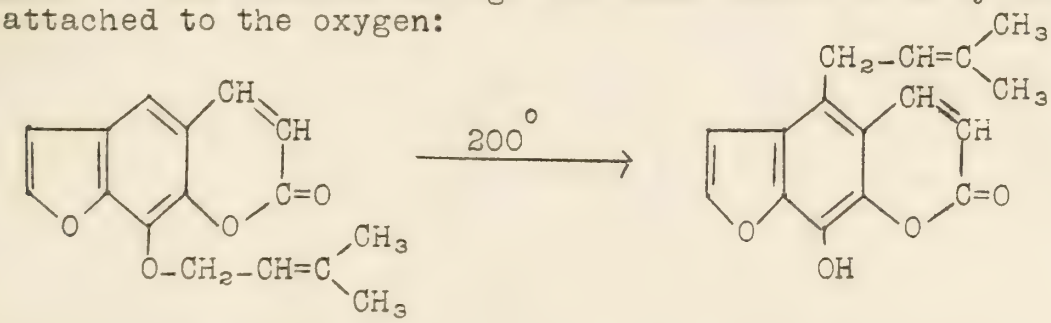
Lauer also reported a similar abnormal rearrangement in the case of ethyl p-(γ-ethylallyloxy)-benzoate.

Mumm has recently published data on several para rearrangements which show that the wandering group sometimes suffers an inversion and sometimes does not. Hurd's mechanism provided only for no inversion and so must be discarded for these cases.

At present Mumm prefers a free radical explanation and claims it to be the most satisfactory one in the case of para rearrangement.

Two new techniques have been applied recently to the study of allyl rearrangement products and have proved very useful. Hot mercuric acetate in glacial acetic acid is reduced by the propenyl grouping, $-\underset{R}{C}=CHCH_3$, and not by the allyl grouping, $-CHR-CH=CH_2$. The second is a very sensitive test for a para-rearrangement product. It is limited by the fact that the sidechain must be convertible to a -CHO group, i.e., the compound must first be transformed into a hydroxy benzaldehyde. Copper acetate then precipitates the o-hydroxybenzaldehyde and even very small amounts of the para-compound may be extracted with ether and isolated.

Späth has reported recently that he has met with an interesting case of para-allyl rearrangement in the course of his work on the natural product, imperatorin, in which the wandering group becomes attached to the nucleus through the same carbon atom by which it was attached to the oxygen:



imperatorin alloimperatorin

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Reported by Elwood H. Ensor
January 17, 1940

HYDROGEN FLUORIDE AS A CONDENSING AGENT IN ALKYLATION REACTIONS

Simons and Archer -- Pennsylvania State College
Calcott, Tinker, and Weinmayr -- du Pont and Company

Many catalysts have been used for alkylation and acylation of aromatic compounds. The use of metallic halides in Friedel-Crafts syntheses is familiar. Acid catalysts as sulfuric acid, phosphoric acid, phosphorus pentoxide and, more recently, anhydrous hydrogen fluoride have also been used. Although this report is concerned primarily with hydrogen fluoride, some mention of the other acidic catalysts will be made.

Hydrogen fluoride has been shown to be a useful catalyst for organic reactions. Simons and Archer believe that an explanation for its apparent uniqueness can be found in its physical properties. Despite its apparent weakness in aqueous solution, it is a powerful acidic substance. This property of donating protons makes it a useful reagent for organic reactions such as polymerization and rearrangements in which a positive organic ion is the intermediate.

Its unusual ability to form addition compounds probably accounts for its usefulness in reactions involving aromatic compounds. A complex intermediate similar to those postulated for reactions using aluminum chloride may be the active agent.

The fact that the other hydrogen halides are insoluble in it accounts for the reactions in which they are eliminated.

The reactions using hydrogen fluoride will be taken up by classes of reactants.

I. Olefins:

Aromatic hydrocarbons and their derivatives may be alkylated by olefins in the presence of hydrogen fluoride at 0°C. The reaction goes best for olefins containing three or more carbon atoms. The amount of catalyst may be varied within wide limits without affecting the yields. The expected products were obtained, very often mixtures of mono-, di-, and higher substituted derivatives. There were no migrations of groups or rearrangements of the carbon chain. Diisobutylene, however, gave tertiary butyl derivatives rather than octyl derivatives.

Ipatieff stated that in the case of condensations using sulfuric acid there are three completing reactions: (1) alkylation of the aromatic compound, (2) polymerization of the olefin, and (3) reaction of the olefin with the acid to form an ester. Since hydrogen fluoride has been shown to polymerize olefins and add to double bonds, a similar competition might be expected here. However, Simons and Archer found no evidence of side reactions.

Phosphoric acid has been used successfully as a catalyst in these reactions by Ipatieff. The reactions must be carried out at 200-300° and under pressure. Truffault states that both phosphorus pentoxide and phosphoric acid cause polymerization of the olefin at ordinary temperature, rather than alkylation.

Phenols and their ethers have been alkylated smoothly by olefins in the presence of phosphoric acid. At moderate temperatures one alkyl group is introduced ortho to the hydroxyl group.

Phosphorus pentoxide dispersed on charcoal by cresol has been used successfully as catalyst for alkylation reactions at temperatures of 200-250° and 40 atm. pressure.

Concentrated sulfuric acid permits alkylation by olefins at ordinary temperatures. Dilute sulfuric acid (80%) catalyzes polymerization of the olefin.

II Halides:

Hydrogen fluoride is the only acid catalyst which will bring about condensations with aliphatic halides. Tertiary chlorides react readily at 0° and atmospheric pressure, while secondary halides require a temperature of 25° and primary halides do not react detectably at either of these temperatures.

When metallic halides are used as catalysts in these reactions, tars are formed due to condensations of the aromatic rings. No such residues are formed using hydrogen fluoride. Also carbon tetrachloride may be used as a solvent for the higher aromatic hydrocarbons in these reactions.

The amount of hydrogen fluoride needed here is larger than with olefins due to loss in the escaping gases (HCl). Yields are relatively high.

Hydrogen fluoride also catalyzes reactions between tertiary halides and olefins. A mixture of products is produced but this reaction is significant in that other catalysts as sulfuric acid, aluminum chloride, etc., will not promote it.

III Alcohols and Ethers:

Secondary and tertiary alcohols react readily to give the expected products. Isopropyl and dibenzyl ethers are the only ethers which have been used. Benzyl alcohol polymerizes instead of alkylation.

Larger quantities of catalyst are required for these reactions since it is diluted by the eliminated water. Phenols and their ethers have been alkylated by secondary and tertiary alcohols using phosphoric acid as catalyst. Of the primary alcohols, only those like benzyl give good yields.

IV Acids, Acid Chlorides and Anhydrides:

Carboxylic acids are bases in hydrogen fluoride and as such might be expected to act like alcohols, giving condensation with the elimination of water. This was found to be the case.

Acid chlorides and anhydrides have been used in Friedel-Crafts syntheses and thus they might be expected to react here also.

Reactions using these compounds as acylating agents must be carried out in a copper bomb at temperatures of 80-100°. Larger amounts of catalyst must be used here because it is diluted by the water formed and also it forms addition complexes with oxygen containing compounds.

V Esters:

Alkylation of aromatic compounds by esters has been reported recently by Bowden, using aluminum chloride, and by McKenna and Sowa, using boron trifluoride as catalysts. Hydrogen fluoride has been found to bring about this reaction also. The reaction may be represented:

$$RCOOR' + C_6H_6 \longrightarrow RCOOH + C_6H_5R''$$

where R" may be the same as R' or a rearranged form thereof. As it has been found that acids can acylate aromatic compounds in the presence of hydrogen fluoride, some ketone might be expected. This actually proved to be the case. Bowden in his study of this reaction, using aluminum chloride did not find any carbonyl compounds although he made a special effort to do so.

McKenna and Sowa postulated that this type of alkylation proceeded through two stages: (1) formation of an olefin and acid from the ester, (2) reaction of olefin with the aromatic compound to give the alkylated product. An alternative mechanism, which they rejected, involved a metathesis between the ester and the aromatic compound. Their rejection is based on the fact that esters of straight-chain alcohols do not give normal alkylations.

Simons and Archer propose another mechanism involving ionization of the ester to produce a positive alkyl ion and a negative acyl ion. This reaction would be assisted by the strong acid properties of the solvent, which would neutralize the acyl ion to form the carboxylic acid which would in turn react with the solvent.

$$RCO_2R' + 2HF \rightleftharpoons RCOOH_2^{+} + R'^{+} + 2F^{-}$$

As the charge on the alkyl ion would not be localized reaction would occur with the carbon atom which would result in the greatest reduction of free energy. A rearranged product could be formed.

The fact that benzyl acetate will react with benzene to give, in presence of hydrogen fluoride, diphenylmethane in yields of 75% seems to be strong evidence supporting the ionic rather than the olefin mechanism.

These reactions with esters were carried out under the same conditions as those with acids and acid chlorides.

VI Compounds Containing an Allylic Group:

Reactions were carried out using such compounds as benzyl chloride, cinnamic acid, and allyl alcohol. Allyl chloride has been condensed with benzene in the presence of sulfuric acid to yield β-chloroisopropylbenzene. Allyl alcohol and benzene in the presence of sulfuric acid gave 1,2-diphenylpropane in 32% yield.

Allyl alcohol condenses with phenols and phenol ethers in the presence of phosphoric acid to give polymeric products which are depolymerized to the alkylated derivatives on dry distillation.

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Reported by Edmond Bottorff
January 17, 1940

REACTION OF NITROCHLOROBENZENES WITH POSITIVE ETHYLENES

Wizinger and Coenen -- Bonn and Zurich Universities

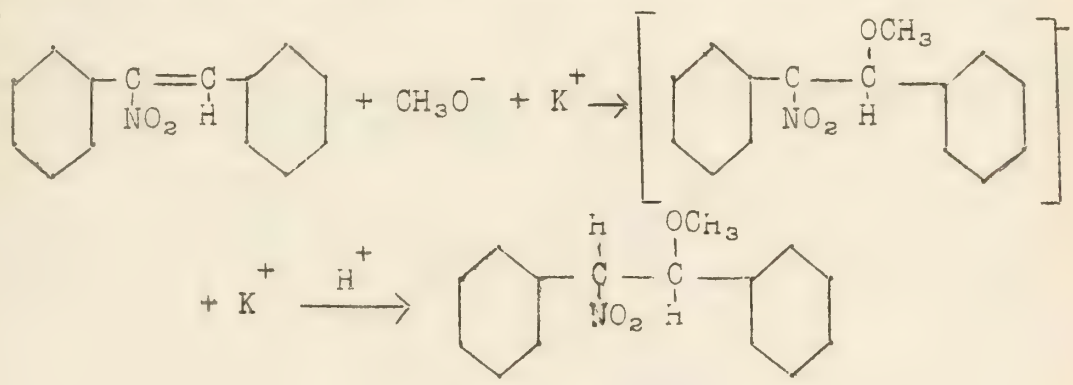
In o- and p-nitrochlorobenzene, much more in 2,4-dinitrochlorobenzene and especially in 2,4,6-trinitrochlorobenzene, the chlorine atom is very active; it is easily replaced by the groups, $-OCH_3$, $-OH$, $-SH$, $-SO_3Na$, $-NH_2$, etc. The reagents used to effect this displacement are alkali alcoholates, alkalies, sodium hydrosulfide, sodium sulfite, ammonia, etc. Secondary amines may be used if they are basic enough. In the case of the di- and trinitro compounds, the reaction takes place at the temperature of boiling water. These anions which are capable of replacing the chlorine atom have in common the property that all possess a strong proton affinity.

$$CH_3O^- + H^+ \longrightarrow CH_3OH$$

$$SH^- + H^+ \longrightarrow HSH$$

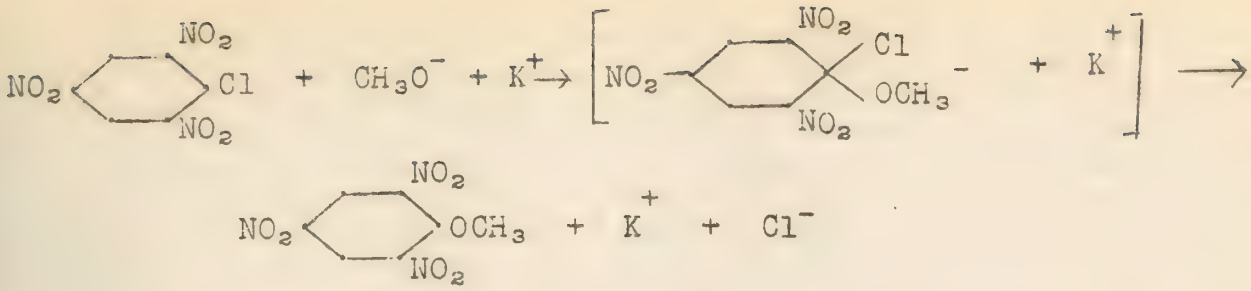
$$NH_3 + H^+ \longrightarrow NH_4^+$$

Similarly there are other atoms which possess a strong electron affinity. Examples are the β-carbon atoms of the α-nitro ethylenes and the corresponding carbon atoms of aromatic nitro compounds. Thus α-nitrostilbene on treatment with potassium methylate yields a potassium salt.

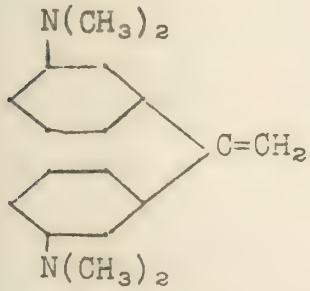


The reaction proceeds in an analogous manner with aromatic nitro compounds. Thus trinitrobenzene forms a red salt with potassium methylate. The use of trinitrobenzene as an indicator is based on the fact that it adds the hydroxyl ion with the formation of a red color.

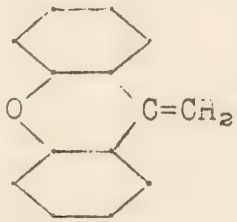
The addition of potassium methylate, sodium hydroxide, etc., to trinitrochlorobenzene and to a lesser extent o- and p-nitrochlorobenzene is similar. The chlorine atom in this case can be ionized as the chloride ion.



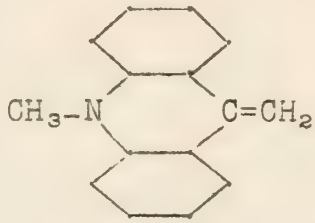
R. Wizinger and workers have studied α,α-disubstituted ethylenes. An ethylene of this type is said to be positive if it has a strong proton affinity, indeed the greater the proton affinity, the stronger is the positivity of the ethylene. The positivity of the α,α-disubstituted ethylene may be increased by substituting on the α-substituents such groups as CH_3O-, HO-, NH_2, CH_3O-C_6H_4-, etc. Examples of weakly positive ethylenes are α,α-diphenylethylene, α,α-dianisylethylene and α,α-diveratrylethylene. Moderately strong positive ethylenes are tetramethyldiaminodiphenylethylene (A), methylenexanthene (B), and N-methyl-9-methylenedihydroacridine (C).



A

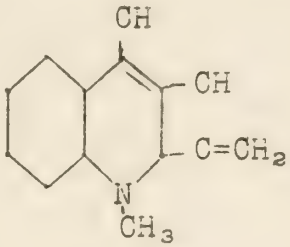


B

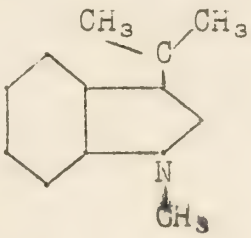


C

Very strongly positive are N-methyl-2-methylenedihydroquinoline (D) and 1,3,3-trimethyl-2-methyleneindolin (E)



D

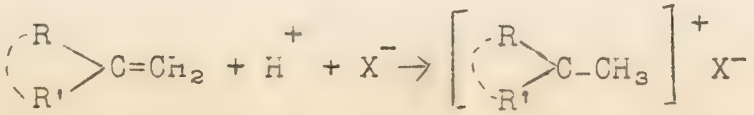


E

Simple aliphatic ethylenes add HX with the formation of non ionic compounds of ester character.

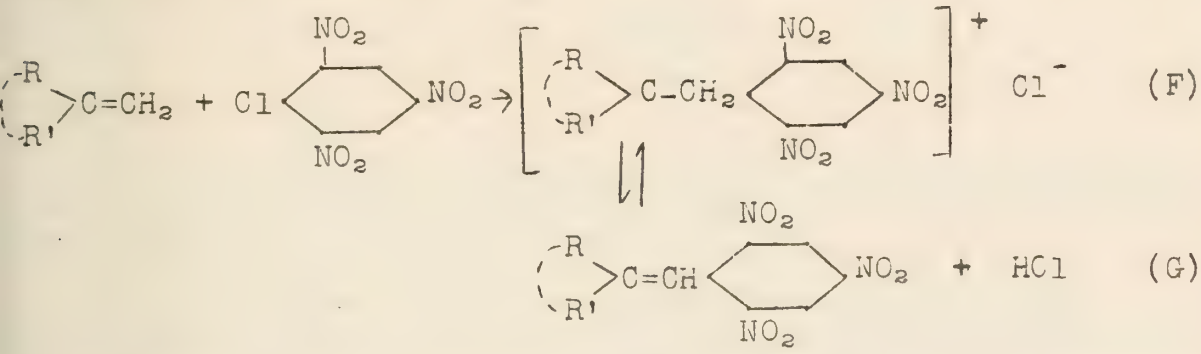
$$CH_2{=}CH_2 + HX \longrightarrow CH_3CH_2X$$

The strongly positive ethylenes in comparison form with HX, ionic addition products.



The molecule, HX, is ionized, the proton adding to the β-carbon atom in a non-ionic linkage, while the anion is linked ionically to the α-carbon atom. The above reaction then, leads to a methyl carbonium salt, rather than to a compound of ester character. α,α-Dianisylethylene, because of its weak positivity, forms methyl carbonium salts only with very strong acids. Compound A, which is more positive forms carbonium salts even with weak acids as acetic. However, only the perchlorate has been isolated. Employing the strongest positive ethylenes leads to methyl carbonium salts of weak acids which can be isolated.

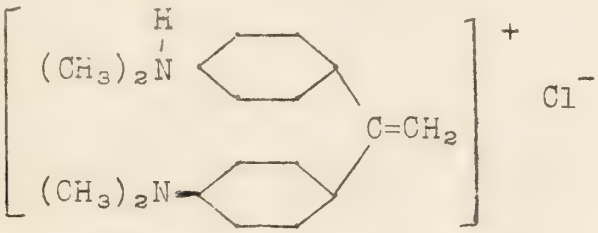
The question now arises if such an ethylene molecule would show all of the reactions typical of a proton acceptor, whether it would react with trinitrochlorobenzene or even with the weaker nitrochlorobenzenes as the strong proton acceptors do. The following reaction might then be expected.



The reactions were carried out simply by heating a benzene solution of the components. For the very strongly positive ethylenes it was found that reaction proceeded according to the following equation

2 moles ethylene + 1 mole picryl chloride $\longrightarrow$ 1 mole picryl ethylene + 1 mole methyl carbonium salt

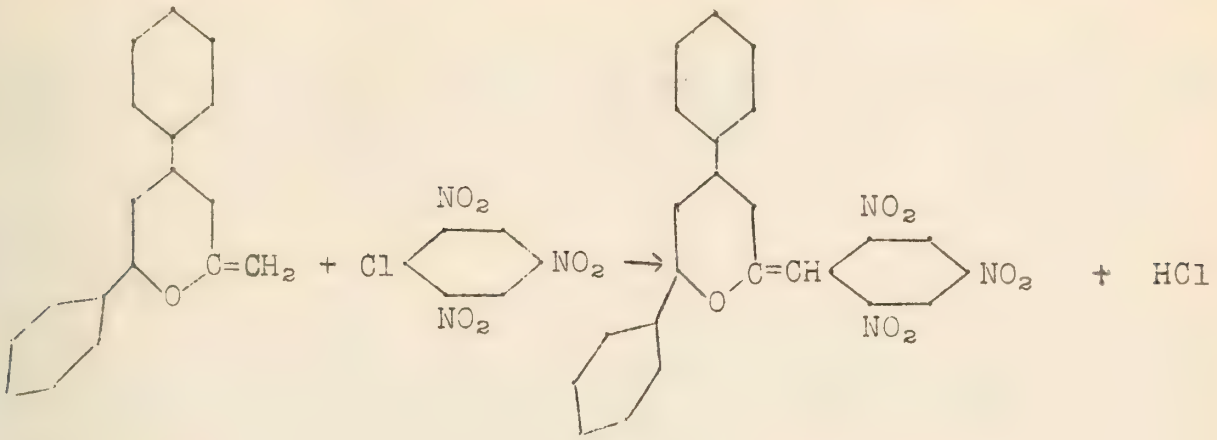
The methyl carbonium salts are insoluble in benzene and drop out of solution. It can be seen that at most a fifty per cent yield of the picryl ethylene is obtainable. The carbonium salt, however, may be easily decomposed to yield the original starting material. In the case of tetramethyldiaminodiphenylethylene a competing reaction takes place forming the colorless ammonium salt.



As expected, the moderately strong down to the weakly positive ethylenes do not form carbonium salts. They react according to the following equation

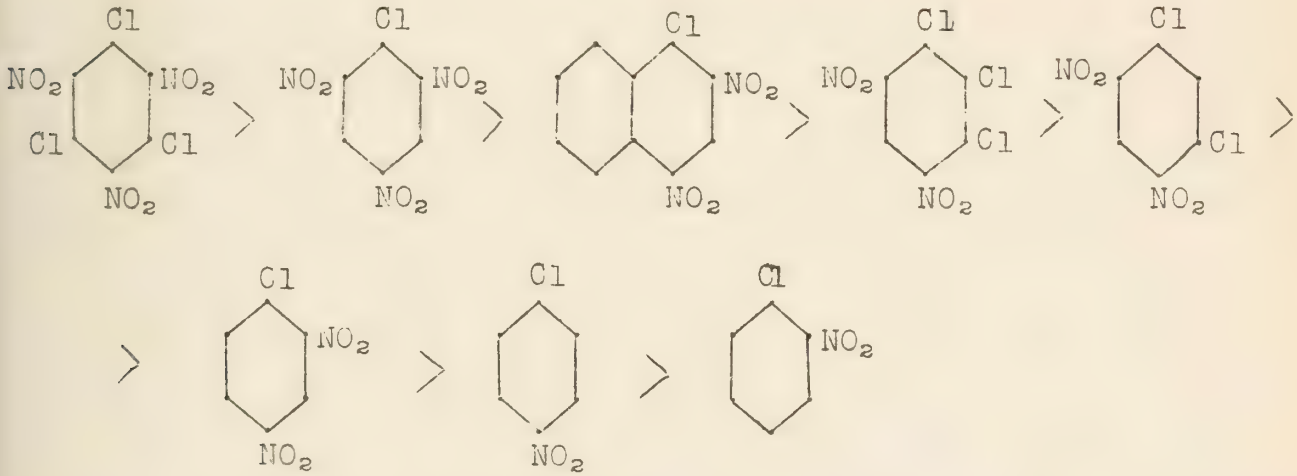
1 mole ethylene + 1 mole picryl chloride $\longrightarrow$ 1 mole picryl ethylene + 1 mole HCl

An example is 2-methylene-4,6-diphenylpyrone. Thus



The introduction of a methyl group in the β-position of the α,α-disubstituted ethylene lends the molecule stability and no reaction with picryl chloride takes place.

The following nitrochlorobenzenes were also employed in this investigation and the order of activity of these compounds was determined. They are listed with decreasing activity.



The yields of the nitrophenylethylenes varied greatly. Reacting tetramethyldiaminodiphenylethylene with the following nitrochlorobenzenes gave yields varying from 0% to 90%

picryl chloride	2,4-dinitrochloronaphthalene
90 %	25 %

2,4-dinitro-1,5,6-trichlorobenzene	2,4-dinitrochlorobenzene
1 %	0 %

The very strongly positive ethylenes reacted with 2,4-dinitrochloronaphthalene giving yields varying from 25% to 70%.

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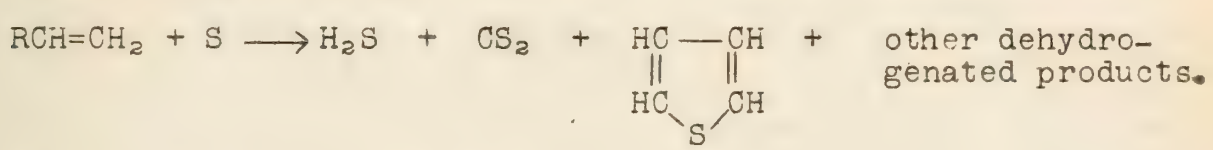
Reported by H. Braus

THE ADDITION OF THIOLS TO OLEFINS

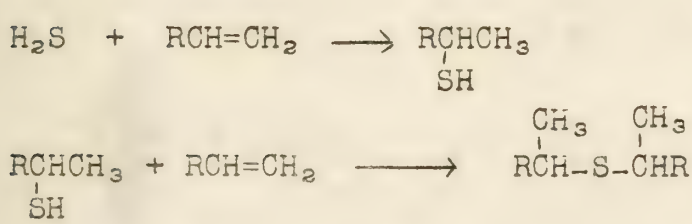
Ipatieff and associates -- Universal Oil Products Co.
E. E. Reid -- Johns Hopkins University.

The addition of sulfur, hydrogen sulfide, and thiols to various olefins has been reported by many investigators. Because of a lack of uniformity of experimental conditions, there have been many conflicting reports as to the structure of the resulting compounds. Recent systematic investigation of the influences involved indicates potential usefulness of this reaction as a means of identification of olefins.

Jones and Reid have investigated the action upon olefins of both sulfur and compounds which readily liberate sulfur, e.g. pyrites and ethyl tetrasulfide. The initial action is the dehydrogenation of part of the hydrocarbon with the production of hydrogen sulfide. The hydrogen sulfide adds to the double bond, forming a mercaptan. This may in turn react with another molecule of olefin to form an alkyl sulfide.



$$RCH{=}CH_2 + S \longrightarrow H_2S + CS_2 + \begin{array}{c} HC{-}CH \\ \| \quad \| \\ HC \diagdown S \diagup CH \end{array} + \text{other dehydrogenated products.}$$

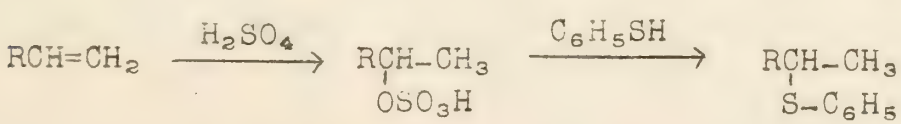


$$H_2S + RCH{=}CH_2 \longrightarrow R\underset{\underset{SH}{|}}{C}HCH_3$$

$$R\underset{\underset{SH}{|}}{C}HCH_3 + RCH{=}CH_2 \longrightarrow R\overset{\overset{CH_3}{|}}{C}H{-}S{-}\overset{\overset{CH_3}{|}}{C}HR$$

In the presence of sulfur the additions follow Markownikoff's rule. All of the olefins examined, with the exception of ethylene, yielded secondary or tertiary mercaptans and sulfides.

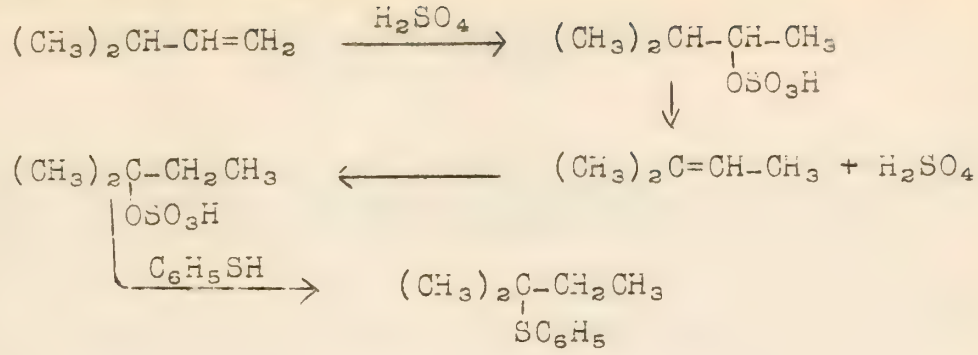
The addition of mercaptans and thiophenols to olefins is catalyzed by sulfuric acid and by organic peroxides. Ipatieff and coworkers have shown that thiophenol, ethyl mercaptan, and thioacetic acid add to ethylenic compounds abnormally, i.e., contrary to Markownikoff's rule, in the absence of sulfuric acid. Jones and Reid, however, attribute this effect to traces of organic peroxides present in the reactants. para-Thiocresol and propylene, when free from peroxides, undergo normal addition in the absence of a catalyst. The addition of a trace of ascaridole produces abnormal addition. The sulfuric acid catalyzed reaction possibly takes place through an alkyl sulfuric acid intermediate:



$$RCH{=}CH_2 \xrightarrow{H_2SO_4} R\underset{\underset{OSO_3H}{|}}{C}H{-}CH_3 \xrightarrow{C_6H_5SH} R\underset{\underset{S{-}C_6H_5}{|}}{C}H{-}CH_3$$

Isopropyl ethylene undergoes isomerization to give a tert.-amyl rather than a sec.-isoamyl sulfide. The following mechanism

may account for this change.



The directive effect of sulfuric acid prevails over that of peroxides when the latter are present in small amounts. Phosphoric acid has little effect since olefins react with it less readily than with thiophenol.

The sulfides themselves are usually liquids or low melting solids but may be converted to solid derivatives suitable for identification purposes. Oxidation with thirty per cent hydrogen peroxide in acetic acid converts many to solid sulfones. Others give satisfactory coordination complexes of the type $(R_2S)_2 \cdot PdCl_2$ and $R_2S \cdot HgCl_2$ when treated with palladous or mercuric chlorides. The thioesters produced by the addition of thioacetic acid may be identified by saponification to mercaptans followed by precipitation of mercuric mercaptides.

The applications and limitations of this reaction in the identification of olefins are being investigated by Ipatieff at the present time. The peroxide catalyzed reaction may prove to be the more useful because of the tendency of sulfuric acid to cause isomerization of certain olefins.

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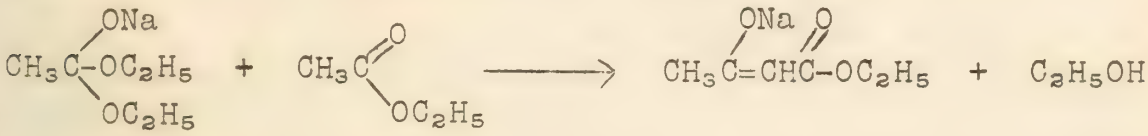
Reported by A. H. Land

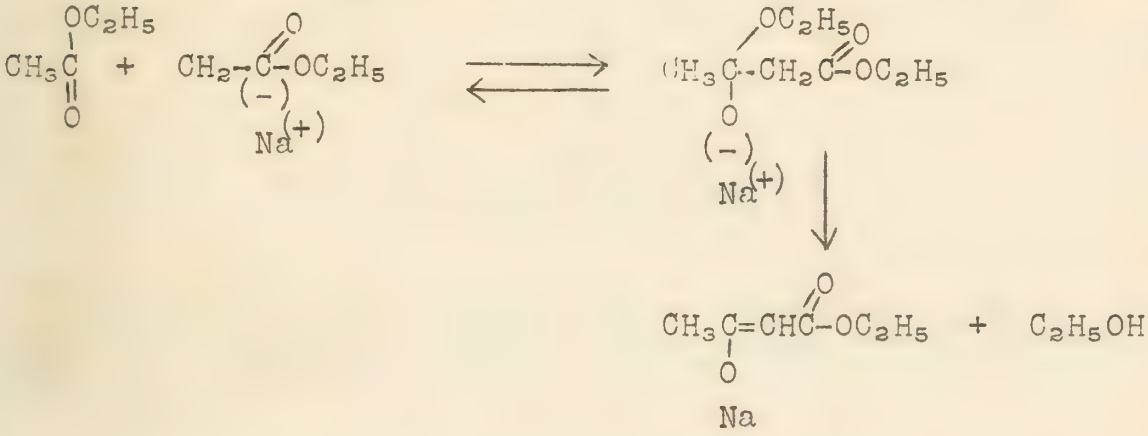
ABNORMAL ACETOACETIC ESTER SYNTHESIS

Tseou -- University of Chekiang
Hongchou, China

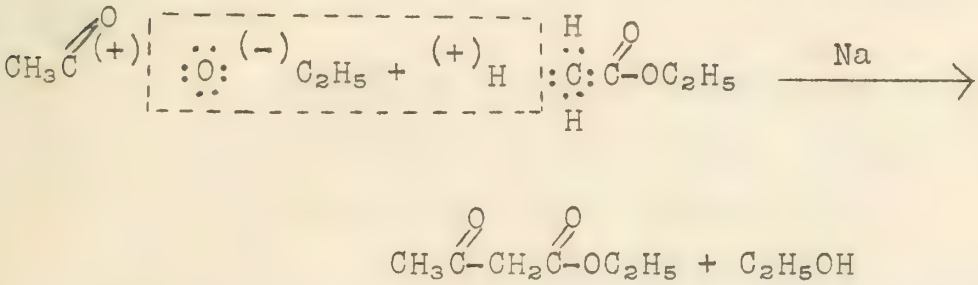
Many mechanisms have been proposed for the synthesis of ethyl acetoacetate from ethyl acetate in the presence of sodium. For example, Claisen postulates the essential step to be:



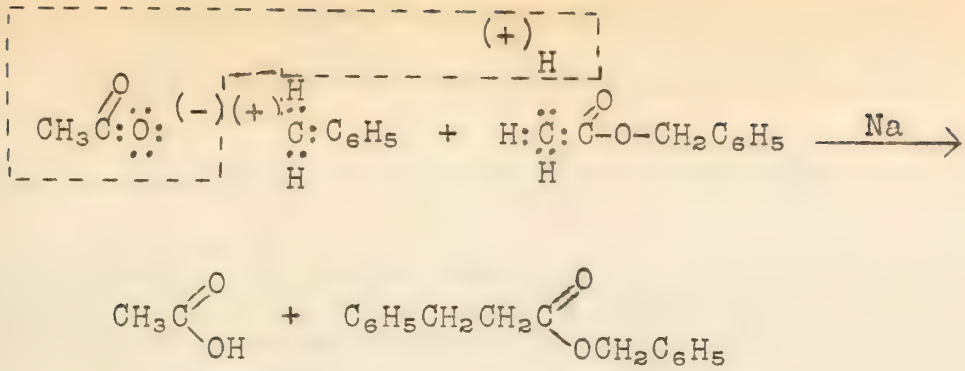
while Arndt and also Hansen explain it essentially as follows:



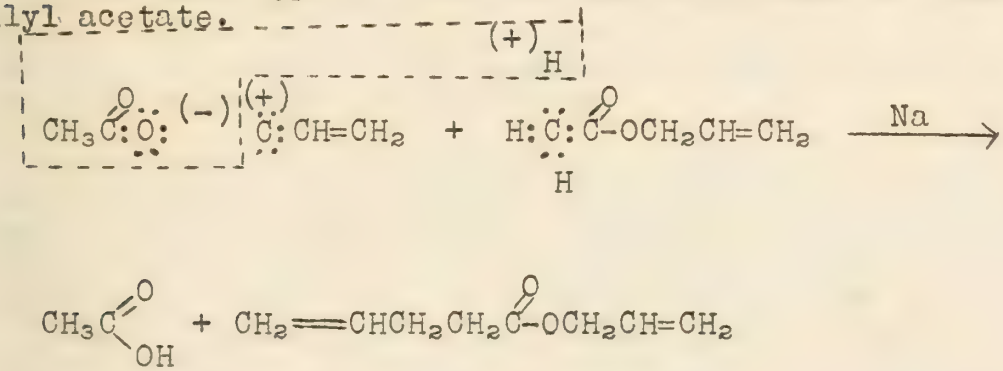
According to Tseou's electronic theory of organic reactions the synthesis of acetoacetic ester takes place in the normal manner because of the relative negative polarity of the oxygen of the ethoxy group in contrast to the polarity of the carbon atom of the carbonyl group. Thus, the electrons are drawn away from the carbon atom and close to the oxygen atom. Also the hydrogen atoms of the CH_3 group are relatively positive, thus tending to split off easily. This may be diagramed as follows:



If, however, the ethyl group is replaced by a group (such as the benzyl radical) that is relatively strongly positive, the electrons will be shifted towards the carbonyl group and the molecule will split between the oxygen and the benzyl group.



This same type of reaction was also found to take place with allyl acetate.



The product was isolated as its hydrolysis products, allylacetic acid and allyl alcohol. An iodoform test on the reaction mixture was entirely negative, showing that no allyl acetoacetate was formed.

When a still more strongly positive radical was used (such as the diphenyl methyl radical) a third type of reaction was observed. It was found that this radical could be directly replaced by sodium with the formation of sodium acetate and the coupling product of two of these radicals.

$$2\ CH_3\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH(C_6H_5)_2 + 2\ Na \longrightarrow 2\ CH_3\overset{O}{\overset{\|}{C}}\text{-}ONa + (C_6H_5)_2CHCH(C_6H_5)_2$$

The tetraphenylethane was isolated in a 70 per cent yield and the remainder of the material was found to be unreacted diphenyl methyl acetate.

Cinnamyl acetate was found to react in the same way.

$$2\ CH_3\overset{O}{\overset{\|}{C}}\text{-}OCH_2CH{=}CHC_6H_5 + 2\ Na \longrightarrow$$

$$2\ CH_3\overset{O}{\overset{\|}{C}}\text{-}ONa + C_6H_5CH{=}CHCH_2CH_2CH{=}CHC_6H_5$$

The 1,6-diphenyl-1,5-hexadiene was isolated partly as such, partly as a dimer, and partly as higher polymers.

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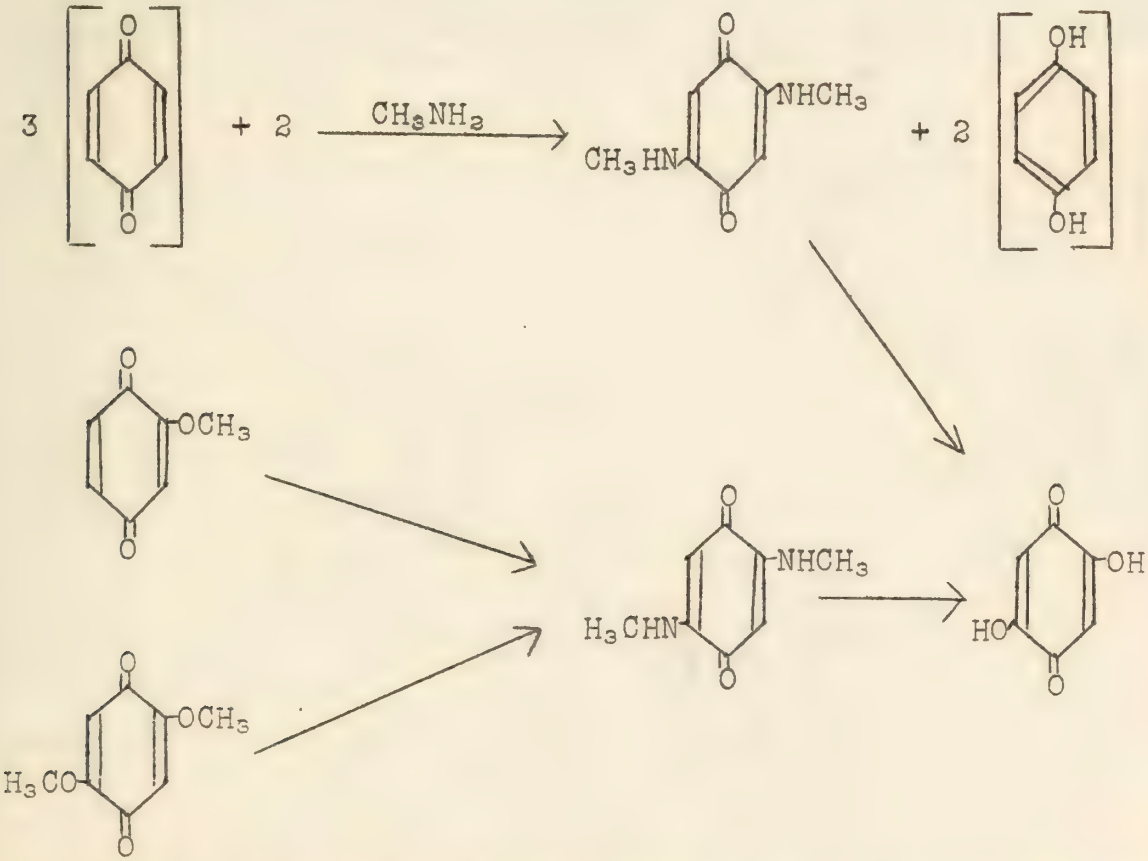
Reported by Bruce Moffett

THE ACTION OF ALCOHOLIC MONOMETHYLAMINE ON DERIVATIVES OF BENZOQUINONE AND TOLUQUINONE

W. K. Anslow and H. Raistrick -- University of London

Spinulosin, which was isolated from the mold Penicillium spinulosum thorn, has been shown by Birkinshaw and Raistrick to be 3,6-dihydroxy-4-methoxy-2,5-toluquinone. This and other similar quinones function in an oxidation-reduction reaction in natural metabolic processes. In trying to synthesize this compound, Anslow and Raistrick discovered an unexpected reaction between monomethylamine and certain methoxytoluquinone derivatives. This led to an extensive study of the reaction of the amine on a number of the methoxy and hydroxy-methoxy derivatives of benzoquinone and toluquinone.

The reaction of methylamine on quinones has been known for many years. It is generally believed that the methylamino group enters the ring by nuclear substitution. bis-Methylamino derivatives, in which the substituents are para to each other, are usually obtained. If the methoxy group is already on the quinone, it may be replaced by a methylamino group with the elimination of methyl alcohol. When nuclear substitution occurs, a mole of the quinol is formed as by-product for every methylamino group that enters the ring.

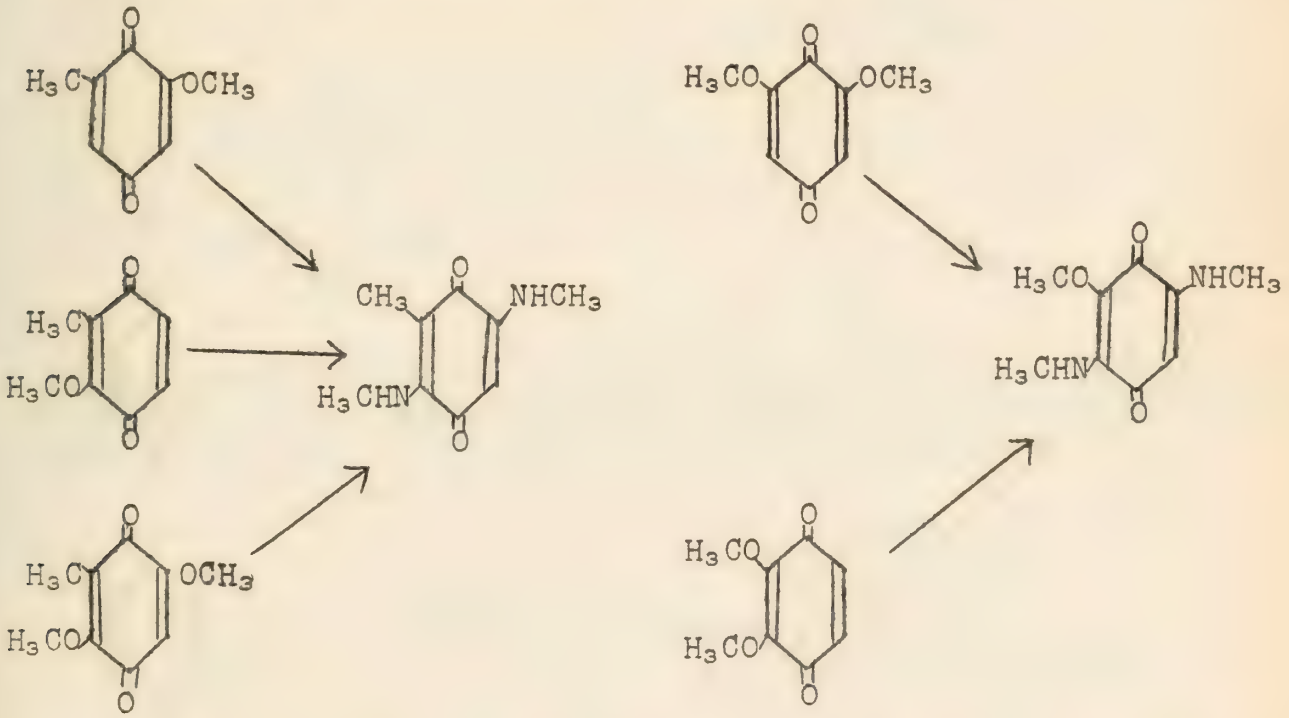


These bis-methylamino derivatives can be hydrolyzed easily to give the corresponding dihydroxyquinones. This method is used often in synthetic work.

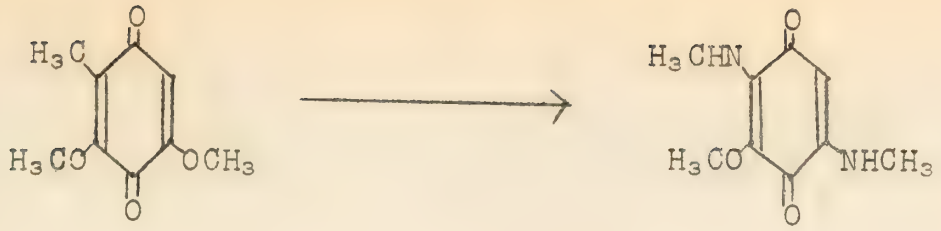
The methoxy- and hydroxy-methoxybenzoquinones and toluquinones used in this investigation were prepared in various ways. Hydroxy and hydroxy-methoxy benzoic acids were decarboxylated to give quinols which were oxidized to the corresponding quinones. Pyrogallol and its methyl ethers were oxidized. In some cases, hydroxy-methoxyquinones were prepared by the hydrolysis of bis-methylamino derivatives of methoxyquinones prepared from other quinones as indicated in this abstract. The Thiele-Winter reaction was also used. This consisted in acetylating a substituted quinone. Both C=O groups, any C-OH groups, and also a nuclear >CH group undergo acetylation.

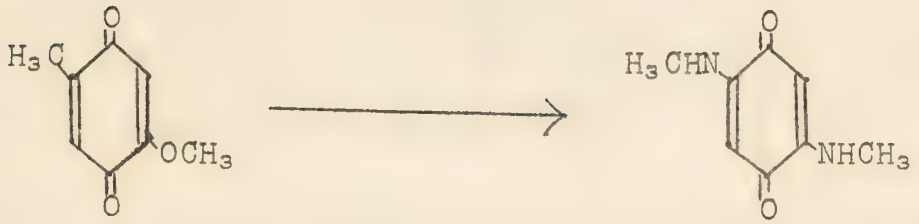
In all the reactions carried out, the quinone was dissolved in ethanol, and a large excess of a 33 per cent solution of monomethylamine in ethanol was added. The methylamino derivatives, being less soluble, crystallized out and were separated and purified. The structures of those derivatives which had not been reported previously in the literature were established by several methods. They were hydrolyzed to hydroxyquinones. These compounds were then reduced by sodium hyposulfite to the corresponding hydroxybenzene compounds. Acetate derivatives were prepared in some cases.

A. Reactions of Methoxyquinones.--Thirteen methoxy derivatives of benzoquinone and toluquinone were prepared, and their reactions with excess monomethylamine were observed. Generally, they followed the normal course of reaction.

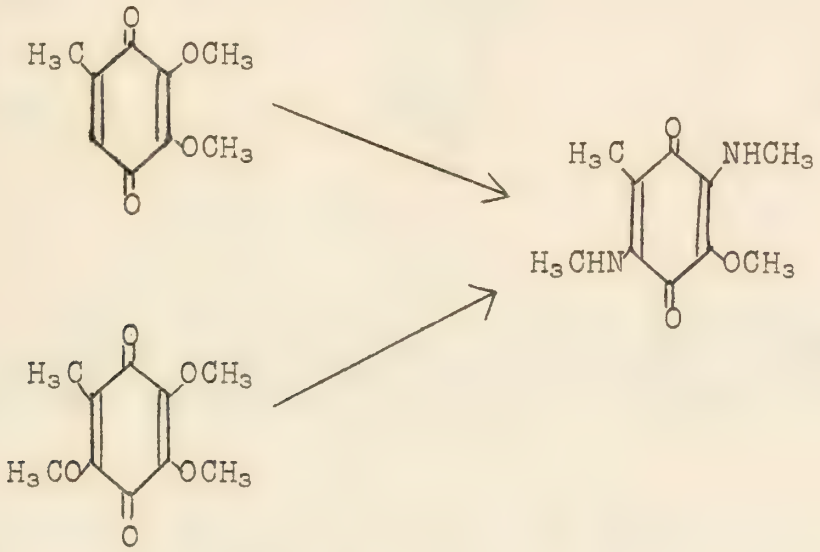


In two compounds, it was observed that the methyl group, when para to a methoxy group, was also removed from the ring.

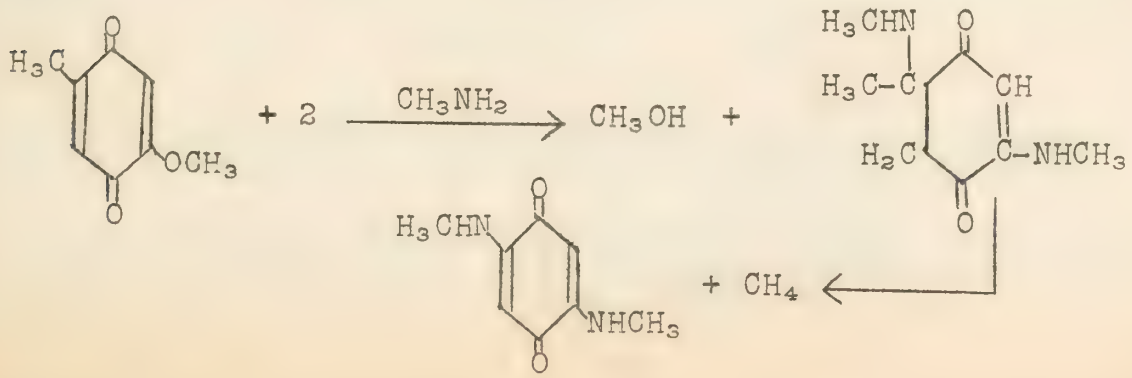




This is an unexpected reaction and up to this point it appears to be general, since in none of the other compounds shown was the methyl group <u>para</u> to the methoxy. However, in the two compounds shown below, the methyl group was not removed.



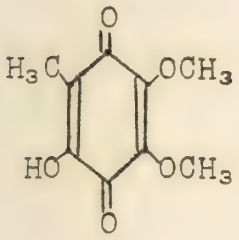
From these results it is difficult to explain the removal of the methyl group. The authors have postulated a 1,2-addition as shown below, followed by removal of a mole of methane.



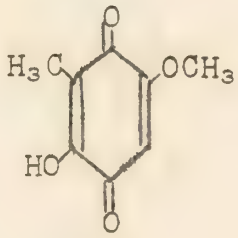
This mechanism would call for a theoretical yield of 100 per cent, and the low yields of 30-40 per cent were not accounted for. The loss of a mole of methane from a substituted quinone upon treatment with an amine had been observed previously by Hoffman and others, so the reaction was not an entirely new one.

It was concluded that the methoxyquinones studied above always gave bis-methylamino derivatives in which the entering groups were para to each other. The reaction may be nuclear substitution, and it may involve the replacement of a methoxy group. In two cases, methyl groups para to methoxy groups were also replaced by methylamino groups.

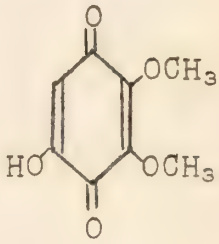
B. Hydroxy-methoxyquinones.--Nine substituted benzoquinones and toluquinones having both methoxy and hydroxy groups were studied. The results showed little regularity, and few generalizations could be made. In three cases, methoxy groups para to hydroxy groups were replaced to give monomethylamino derivatives.



I

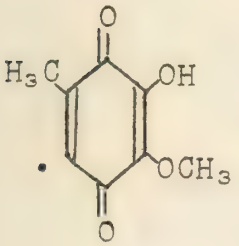


II

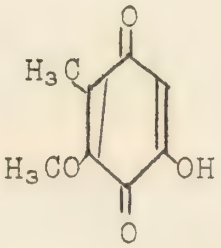


III

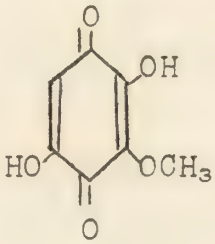
In one case, where there was an open position para to the hydroxy group, nuclear substitution occurred at this point (IV). The other three compounds below gave no reaction at all.



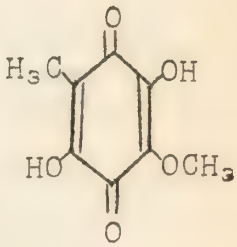
IV



V



VI

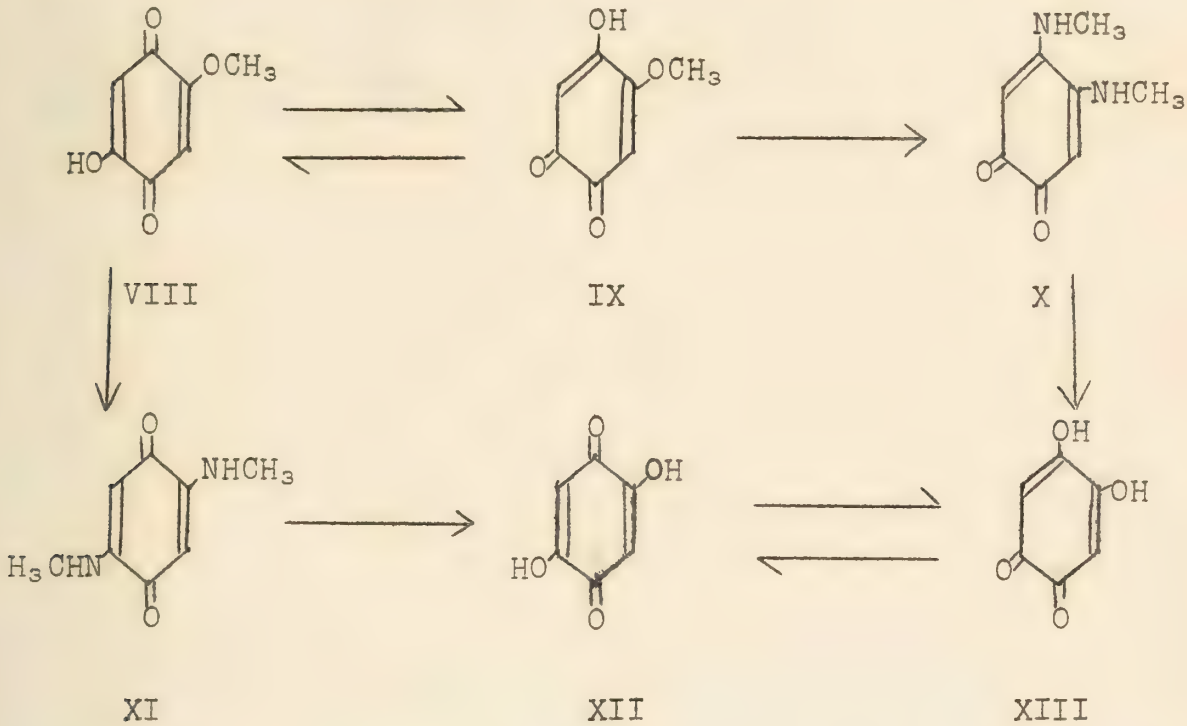


VII

Note that in these compounds, the methyl groups para to methoxy groups are not removed from the ring (I, IV, VII).

Two very irregular reactions were observed. They were explained by the assumption that the para-quinone shifted to its ortho-quinone tautomer during the reaction.

1. 2-Hydroxy-5-methoxy-1,4-benzoquinone (VIII) gave a mixture of two bis-methylaminobenzoquinones, each having the same empirical formula, and each giving 2,5-dihydroxy-1,4-benzoquinone (XII) on hydrolysis.



The melting points and solubilities of the two derivatives (X and XI) were quite different. Compound XI is only slightly soluble in dilute H_2SO_4, because an adjacent C=O group neutralizes each methylamino group. Compound X is soluble in H_2SO_4 and even in water. The products of hydrolysis of both compounds are the same because they are tautomers (XII, XIII).

2. 6-Hydroxy-4-methoxy-2,5-toluquinone gave a bis-methylamino derivative which on hydrolysis gave the same compound that was obtained from 3,4-dimethoxy-2,5-toluquinone. This compound was found to be spinulosin (3,6-dihydroxy-4-methoxy-2,5-toluquinone).

The intermediate bis-methylamino derivatives of the two compounds were quite different, although they had the same empirical formula. It was shown that the former compound underwent a tautomeric shift, as did compound VIII in the above diagram, before reacting.

Further experiments are in progress on a number of substituted quinones, and other publications will appear in the near future.

These reactions offer a useful synthetic method for preparing hydroxyquinones and polyhydroxy benzene compounds.

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Reported by R. B. Wearn

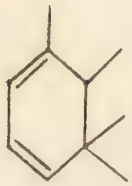
THE ADDITION OF MALEIC ANHYDRIDE TO TERPENE HYDROCARBONS

Kurt Hultzsch --„The Research Department of Dr. Kurt Albert,
Amoneburg bei Wiesboden-Biebrich

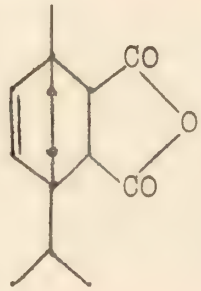
It was found that the terpene hydrocarbons with conjugated double bonds add to maleic anhydride easily and rapidly with a liberation of heat according to the principle of the normal Diels-Alder reaction. In this manner will react terpenes such as: α-phellandrene (I); α-terpinene (II); α- (III) and β-pyronene (IV). Both of the latter are pyrolysis products of α-pinene. Compound X represents the addition product with α-terpinene.


I


II


III


IV



X

However, Hultzsch found that terpene hydrocarbons with no conjugated double bonds also gave addition compounds with maleic anhydride, the two constituents being present in the ratio of 1:1. The purpose of this work was to attempt to determine the reaction mechanisms in these "abnormal" addition reactions.

The terpenes with unconjugated double bonds combine much more slowly and difficultly than do those with conjugated systems and the products are much harder to isolate and crystallize--since a large amount of tarry product is also formed. The yields of crystalline products are very low (10-20 per cent of the tarry residue from the reaction).

Crystalline addition products were produced from: α-pinene (V); limonene (VI); terpinolene (VII); Δ^3- (VIII) or Δ^4-carene (IX). These products all had the same composition as the addition products of I-IV.


V


VI


VII


VIII

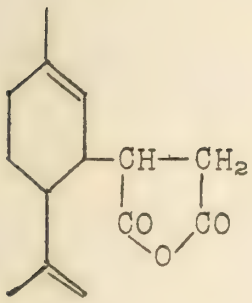

IX

If maleic acid is used instead of maleic anhydride, it was found that a different reaction occurred in the case of the above unconjugated terpenes. In the presence of maleic acid, they undergo a very rapid transformation into α-terpinene and then the normal Diels-Alder reaction occurs with a strong evolution of heat. This reaction also goes for terpene alcohols or other oxidized terpene groups which can split off water.

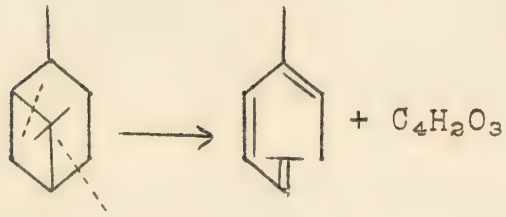
Two different ways by which addition of maleic anhydride to unconjugated terpenes may occur can be thought of:

1. Addition by hydrogen displacement to form substituted succinic acids, as represented by XI.

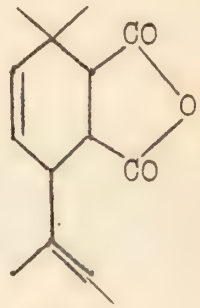
2. The breaking of the terpene structure by the action of maleic anhydride in the heat to form conjugated compounds which will then undergo normal addition as represented by V⟶XII⟶XIII and XIV. The possibility of this type of mechanism is increased by the fact that Arbusow has shown the formation of an acyclic hydrocarbon, allo-ocimene, through catalytic pyrolysis of isomeric α-pinene.



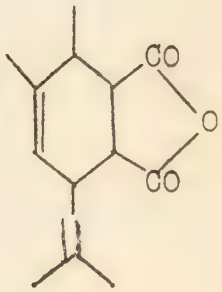
XI



V XII



XIII



XIV

In order to study the latter type of reaction, the maleic anhydride addition product of allo-ocimene was prepared and compared to the addition compounds of V-IX. Allo-ocimene was prepared by pyrolysis of α-pinene at 350° C. according to the method of Arbusow. It has not yet been determined which of the two possible addition compounds (XIII and XIV) is obtained.

The allo-ocimene—maleic anhydride addition compound exhibited some interesting properties:

1. Strong tendency to add water to its double bonds and to lactonize with one or both double bonds. The dilactone will form even in a glacial acetic acid-$ZnCl_2$ solution.

2. Several transformation products were produced from it, the structures of which were not clear.

3. Three isomeric acids (probably cis-trans isomers) were produced.

This addition product was not identical with any of the addition compounds of V-IX, although it was quite similar to them in some respects.

The evidence supporting hydrogen substitution of the maleic anhydride appears to be much stronger than that supporting the second method of reaction. The chief evidence is as follows:

1. Addition compounds of V-IX cannot be transformed into trans acids.

2. They do not form anhydrides as readily as the addition compounds of I-IV.

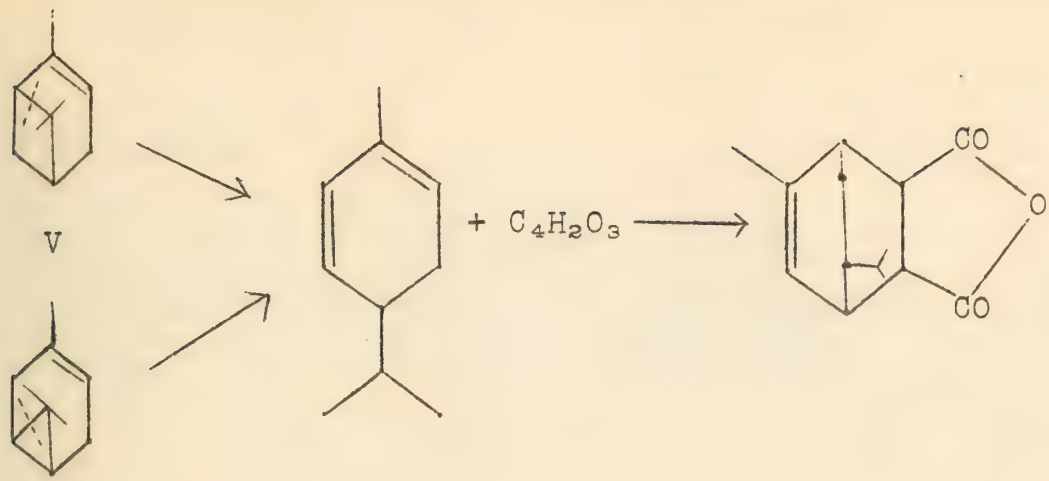
3. The addition compounds of optically active, nonconjugated terpenes are still optically active. Thus, the addition compound of ℓ-limonene rotates left and that of the corresponding d-compound is dextro-rotatory. If this addition had occurred through a ring cleavage and consequent Diels-Alder addition, the compound would not be optically active.

4. The undistillable tarry residue left behind in the reaction mixtures are found usually to have added somewhat more than one mole of maleic anhydride per mole of terpene. These are undoubtedly polymers of the monomeric addition product which have added more maleic anhydride. Thus, further addition is best explained by addition through hydrogen displacement.

5. The addition compounds of α-pinene and carene show only one double bond like the terpene itself. Limonene and terpinolene give addition compounds with two double bonds.

Thus, it was definitely established that the most important type of addition to nonconjugated terpenes is through hydrogen displacement.

In this investigation, another type of addition was discovered. It was found that bicyclic compounds such as α-pinene and carene rearranged through the rupture of a three- or four-membered ring to conjugated systems which underwent normal Diels-Alder addition. This reaction occurs only to a limited extent--the main reaction being substitution.



In the case of α-pinene the addition product was proved to be identical with that of α-phellandrene by mixed melting point determination.

Thus, there are four different ways in which maleic anhydride can react with the terpenes:

1. Terpenes with conjugated double bonds undergo a normal Diels-Alder addition.

2. A series of terpenes without double bonds rearrange themselves in the presence of maleic acid into α-terpinene and thus in a roundabout manner give a normal diene-addition compound.

3. In the case of bicyclic compounds, V and VIII, the three- or four-membered ring is ruptured producing α-phellandrene which is conjugated.

4. In general, the majority of the terpenes without conjugated double bonds form addition compounds by means of hydrogen substitution, and which are substituted succinic acids. These tend toward polymerization in the hot and can hereby add additional maleic anhydride.

The speed of addition of maleic anhydride to unconjugated terpenes varies considerably. It increases, for example, in the following order: α-pinene --- limonene --- terpinolene. The latter reacts with a liberation of heat as soon as the temperature reaches 160°. There are some terpenes which do not react with maleic anhydride under the same conditions. Examples are camphene and camphor.

The various terpene--maleic anhydride addition compounds are claimed to be of technical value in the varnish and lacquer industries. It has also been shown that they could be of importance in the determination of terpene fractions.

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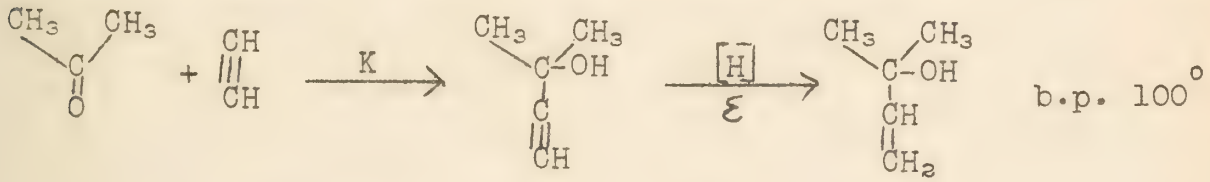
Reported by S. B. Speck

SYNTHESES IN THE TERPENE SERIES

A. E. Favorsky and A. I. Lebedeva
U.S.S.R.

Favorsky and Lebedeva have perfected a method whereby they treated acetylene and ketones with powdered potassium and obtain acetylenic alcohols in yields of 80-90 per cent. Electrolytic reduction in alkaline solution produced 95 per cent of the ethylenic alcohol and 5 per cent of the saturated alcohol. For example:



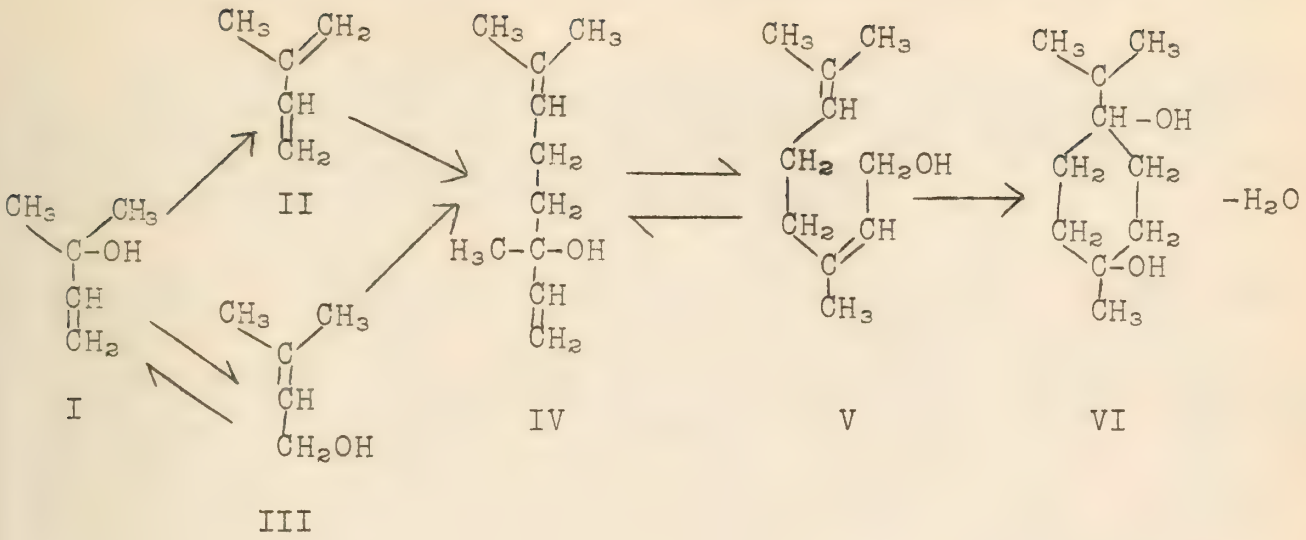
When the electrolysis was carried out in dilute sulfuric acid solution, there resulted a complicated mixture of products.

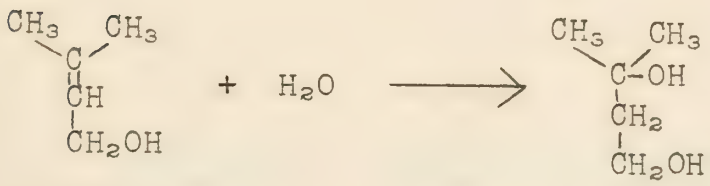
In order to explain these results, the authors assumed that the reduction proceeded normally, but the ethylenic alcohol, in the presence of the sulfuric acid, produced the complicated mixture already mentioned. This proposition was tested by studying the immediate action of sulfuric acid on the tertiary ethylenic alcohol which was obtained in the alkaline reduction:

A solution of dimethylvinylcarbinol (I) in 20 per cent sulfuric acid, left at ordinary temperatures separated into two layers at the end of four to five days. The upper layer contained <u>isoprene</u> (II) (1.5 per cent based on the weight of dimethylvinylcarbinol used), the original <u>dimethylvinylcarbinol</u> (40 per cent), <u>isobutenylcarbinol</u> (III) (no yield reported - undoubtedly, there was a reversible allylic rearrangement of one alcohol to the other) and <u>linalol</u> (IV), during the distillation of which the odor of <u>geraniol</u> (V) was detected. The fractions boiling higher than 195-200° have not as yet been fully investigated.

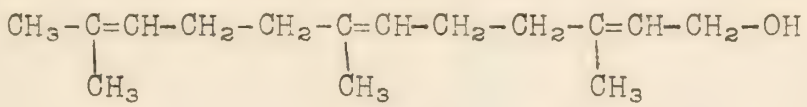
The aqueous layer contained dimethyltrimethyleneglycol (VII) and terpene hydrate (VI) (10 per cent yield).

It seems probable that these transpositions may be represented by the following scheme:



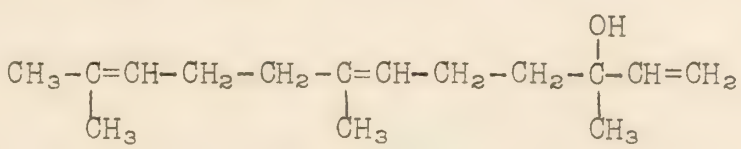


The two combinations, dimethylvinylcarbinol-isobutenylcarbinol and linalol-geraniol represent two pairs of isomers. The first has been shown by the authors to be an example of the allylic rearrangement. By analogy, one would expect the latter pair to comprise a similar equilibrium. However, geraniol would be formed if the isobutenylcarbinol added 1-4 to isoprene instead of 3-4 to form linalol. If geraniol were then to add 1-4 to isoprene the product would be a sesquiterpene, farnesol (VIII):



VIII

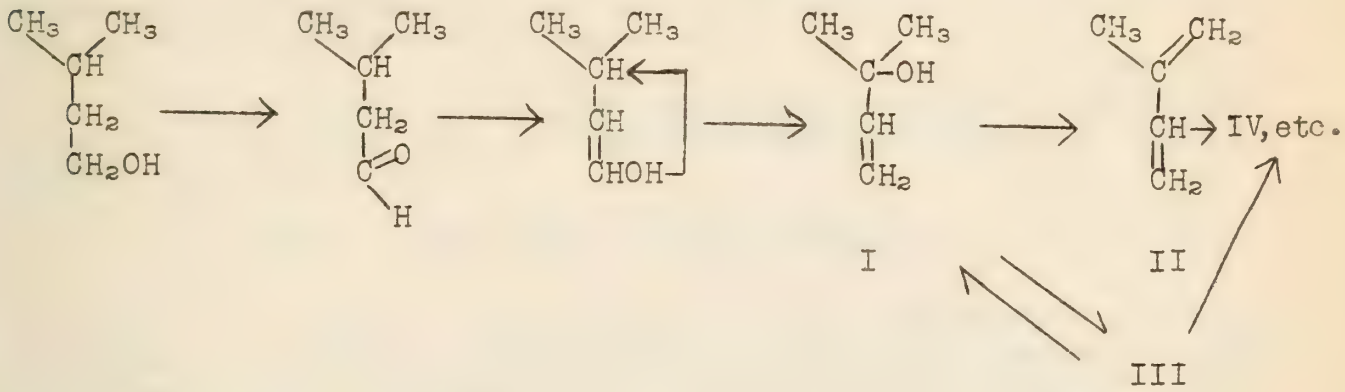
and if it were to add 3-4 to isoprene, the product would be the sesquiterpene, nerolidol (IX):



IX

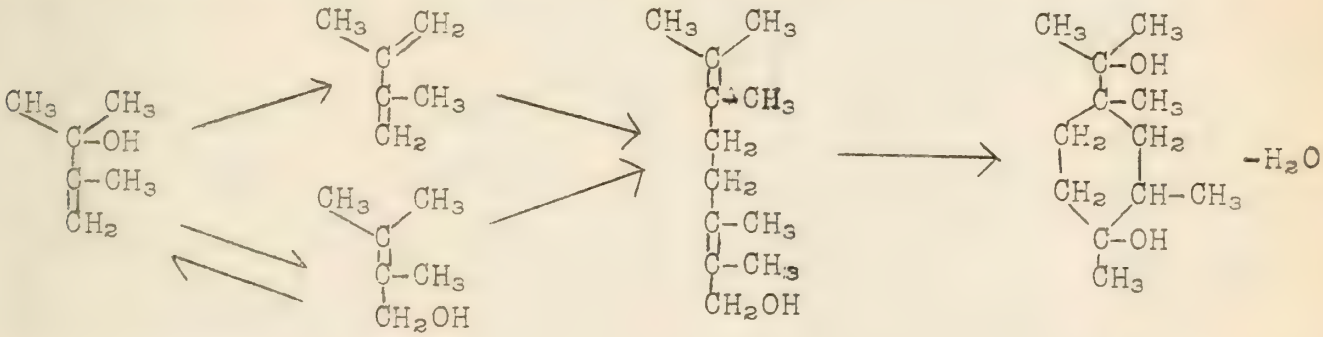
If the mechanism suggested by the authors is correct, these sesquiterpenes should be isolated from the higher-boiling fractions which have already been mentioned.

This work leads to speculation as to the origin of the terpenes in the plant kingdom. If one accepts the theory that hydrolysis of the proteins present form leucine which in turn forms isoamyl alcohol and isovaleraldehyde, then the beginning of the process is perhaps represented by the following scheme:



The process is initiated by acid catalysts which set off the cycles leading to the formation of the more complicated products.

In conclusion, it is interesting to consider the question: Why does nature produce only those terpenes which contain a multiple of five carbon atoms? Is it because the essential starting materials are not available or is it because they are not capable of taking part in such a cycle? All indications point to the first answer and in order to prove this point conclusively, Favorsky and Lebedeva are now attempting to synthesize, according to their method, a compound C_{12} (X) which will be very closely related to the terpenes:



X

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Guinzberg and Ivanov, J. Chem. Gen. Russe, 62, 1991 (1930)

Reported by A. I. Rachlin

α-CHLOROMETHYLATION

Not until 1920 did there appear any systematic study of attempts to introduce chloromethyl and bromomethyl groups into the aromatic nucleus.

Grassi-Cristaldi and Maselli (1898) were the first to show that the product obtained by the action of hydrochloric acid on paraformaldehyde reacted with benzene in the presence of aluminum chloride to yield benzyl chloride and diphenylmethane. In 1920 Stephen and coworkers described the preparation of benzyl chloride and related compounds by the direct introduction of the chloromethyl group into an aromatic nucleus.

It has been shown that the aqueous hydrochloric acid-formaldehyde or hydrochloric acid-paraformaldehyde mixtures contain δ-dichloromethyl ether.

$$ArH + ClCH_2OCH_2Cl \xrightarrow{ZnCl_2} ArCH_2Cl$$

The formation of chloromethyl aromatic compounds is usually accompanied by the production of a diarylmethane derivative, which is formed by the condensation of the chloromethyl compound with the original aromatic compound. The latter reaction depends on the dehydrating agent used. Zinc chloride favors the formation of only small amounts of diarylmethane derivatives while aluminum chloride and sulfuric acid at higher temperatures cause the formation of larger quantities of the substituted methane.

Table I is a brief summary showing some of the types of compounds for which this reaction is useful.

TABLE I

Starting Compound	Chloride Obtained	
Benzene	Benzyl chloride	
Toluene	p-Methyl benzyl chloride and di-p-tolylmethane	
o-Xylene	ω-Chloro-ψ-cumene	
Chlorobenzene . . . 25°C	p-Chlorobenzyl chloride	50% yield
Chlorobenzene . . . 40°C	4,4'-di-(chlorophenyl)-methane	90% yield
Bromobenzene	p-Bromobenzyl-chloride	45% yield
o-Chlorotoluene	3-Chloro-4-methylbenzyl chloride	
Nitrobenzene	m-Nitrobenzyl chloride	
o-Nitrotoluene	3-Nitro-4-methylbenzyl chloride	
p-Nitrotoluene	2-Methyl-5-nitrobenzyl chloride	
Salicylaldehyde	2-Hydroxy-5-chloromethylbenzaldehyde	
2-Hydroxyphenylacetaldehyde	2-Hydroxy-5-chloromethylphenyl acetaldehyde	

hydrochlorides varied from 57-96 per cent while the yields obtained upon reduction varied from 53-79 per cent.

The use of hydrobromic acid instead of hydrochloric acid serves to introduce the $-CH_2Br$ group and appears to be a general reaction. The introduction of $-CH_2Cl$ and $-CH_2Br$ into benzenoid compounds takes place in the para position. However, a nitro group orients the entering group meta.

The halo compounds are readily convertible to the alcohol, hydrocarbon, aldehyde or acid. Numerous patents have been issued for the halomethylation of various aromatic compounds.

Vavon and coworkers have studied the application of α-chloro- and α-bromomethyl ethers as halomethylation agents on the aromatic nucleus. The rate of reaction varies within wide limits with the functional group of the compound. Me, Et, Pr, OMe, and OPr facilitate the reaction whereas Cl, Br, I, CH_2Cl, COOH, and NO_2 make it more difficult. The halogen derivatives are all readily reduced to the hydrocarbon. Mesitylene, for example, has been progressively halomethylated and reduced to hexamethylbenzene.

The halomethyl ethers are prepared readily by the following reaction:

$$CH_2O + CH_3OH + HX \longrightarrow CH_2XOCH_3 + H_2O$$

Table II contains a review of some of the compounds studied by Vavon.

TABLE II

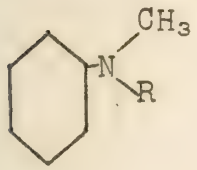
Reactant	Product	Per cent Yield
Toluene	Mixture o- and p-chloromethyltoluene	25
o-Xylene	3,4-Dimethylbenzyl chloride	35
m-Xylene	2,4-Dimethylbenzyl chloride	50
Pseudocumene	2,4,6-Trimethylbenzyl chloride	60
Mesitylene	2,4,6-Trimethylbenzyl chloride	80
Mesitylene	Pentamethylbenzene	80
Mesitylene	Hexamethylbenzene	75
Naphthalene	α-Chloromethylnaphthalene	50
Tetralin	β-Chloromethyltetralin	50
Anisole	p-Methoxybenzyl chloride	60
p-Bromoanisole	2-Methoxy-5-bromobenzyl chloride	40
Ethyl p-methoxybenzoate	2-Methoxy-5-carboethoxybenzyl bromide	95

Possible advantages of the α-halomethyl ether over the CH_2O-HCl mixture as an α-chloromethylating reagent may be as follows: The haloether is easily prepared in a pure form and offers the possibility of using a mutual solvent to dissolve the ether and compound to be halomethylated, thus forming a homogeneous mixture, an advantage over a heterogeneous mixture so often formed when CH_2O-HCl is used. In some cases the ether might be used as the solvent.

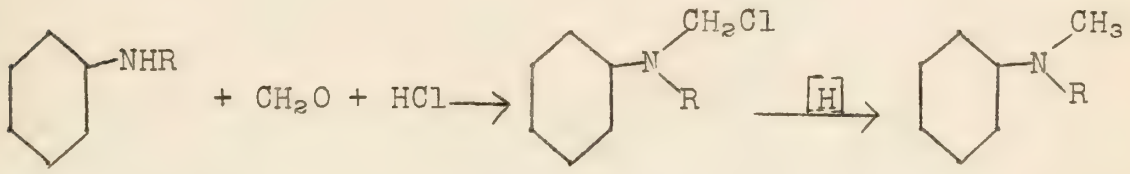
Table I (Cont'd.)

Starting Compound	Chloride Obtained
o-Nitrophenol	3-Nitro-4-hydroxybenzyl chloride
Ethylbenzene	p-Ethylbenzyl chloride
n-Propylbenzene	p-n-propylbenzyl chloride
Naphthalene	α-Chloromethylnaphthalene
Mesitylene	2,4,6-Trimethylbenzyl chloride
α-Methylnaphthalene	1-Methyl-4-chloromethylnaphthalene
β-Methylnaphthalene	1-Chloromethyl-2-methylnaphthalene
Anisole	4-Chloromethylanisole
o-Nitroanisole	2-Nitro-4-chloromethylanisole
p-Methoxybenzaldehyde	3-Chloromethyl-4-methoxybenzaldehyde
o-Methylanisole	3-Methyl-4-methoxybenzyl chloride
m-Methylanisole	2-Methyl-4-methoxybenzyl chloride
p-Methylanisole	2-Methoxy-5-methylbenzyl chloride
2-Isopropyl-5-methylanisole	2-Methyl-4-methoxy-5-isopropylbenzyl chloride

Nuclear and N-Methylations of Secondary Aromatic Amines.--When N-alkyl anilines are used as starting materials and the chlorinated product immediately reduced the product obtained is of the



type. This procedure led in every case to N-methylation, yielding tertiary bases.



In the amines studied the R- groups were as follows: CH_3, C_2H_5, n-C_3H_7, n-C_4H_9 and iso-C_5H_{11}. The yields of the tertiary amines obtained varied from 60-80 per cent.

Isolation of the chlorinated amines as the solid hydrochlorides and vigorous reduction of these compounds led in every case to the corresponding alkyl-p-toluidines, the result being nuclear methylation of the original amine. The amines studied in this series were the same as those considered in the N-methylation series. The yields obtained upon isolation of the crude

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Quelet and Allard, Compt. rend., 205, 238 (1937)
Colonge, Bull. soc. chim., (5) 3, 2116 (1936)
Vavon, Bull. soc. chim., 6, 1025 (1939)

Reported by M. L. Ward

THE STRUCTURE AND SYNTHESIS OF ANONAIN

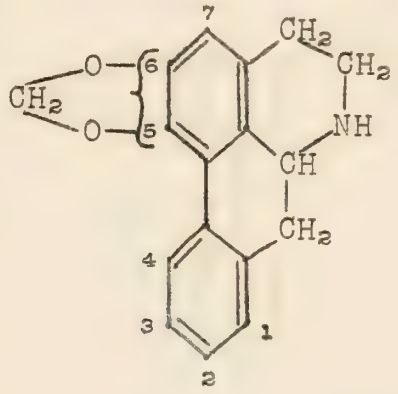
AN APORPHINE ALKALOID

Barger and Weitnauer -- University of Glasgow

Santos in 1930 isolated anonain from the bark of the tropical fruit tree, Anona reticulata L.; he gave $C_{17}H_{16}O_3N$ as its empirical formula, which obviously is incorrect.

From a consideration of the alkaloids found in related plants it was concluded that anonain was probably one of four structural types. The facts that anonain is a secondary, nonphenolic base, that it contains a methylenedioxy group, and that it yields phthalic acid on oxidation, rule out three of these types and leave an aporphine structure as the most likely. Analysis of several derivatives gave an empirical formula, $C_{17}H_{15}O_2N$, which corresponds to a methylenedioxy-aporphine without the N-methyl group, giving provisional formula (I).

Exhaustive methylation follows by oxidation and decarboxylation gave a compound which analyzed for a methylenedioxy phenanthrene, which was, however, not reported in the literature.



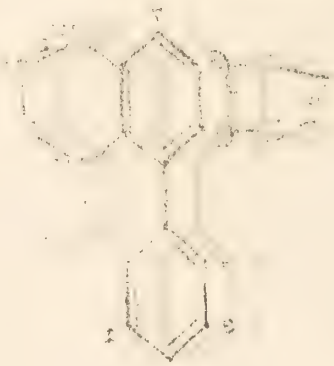
I

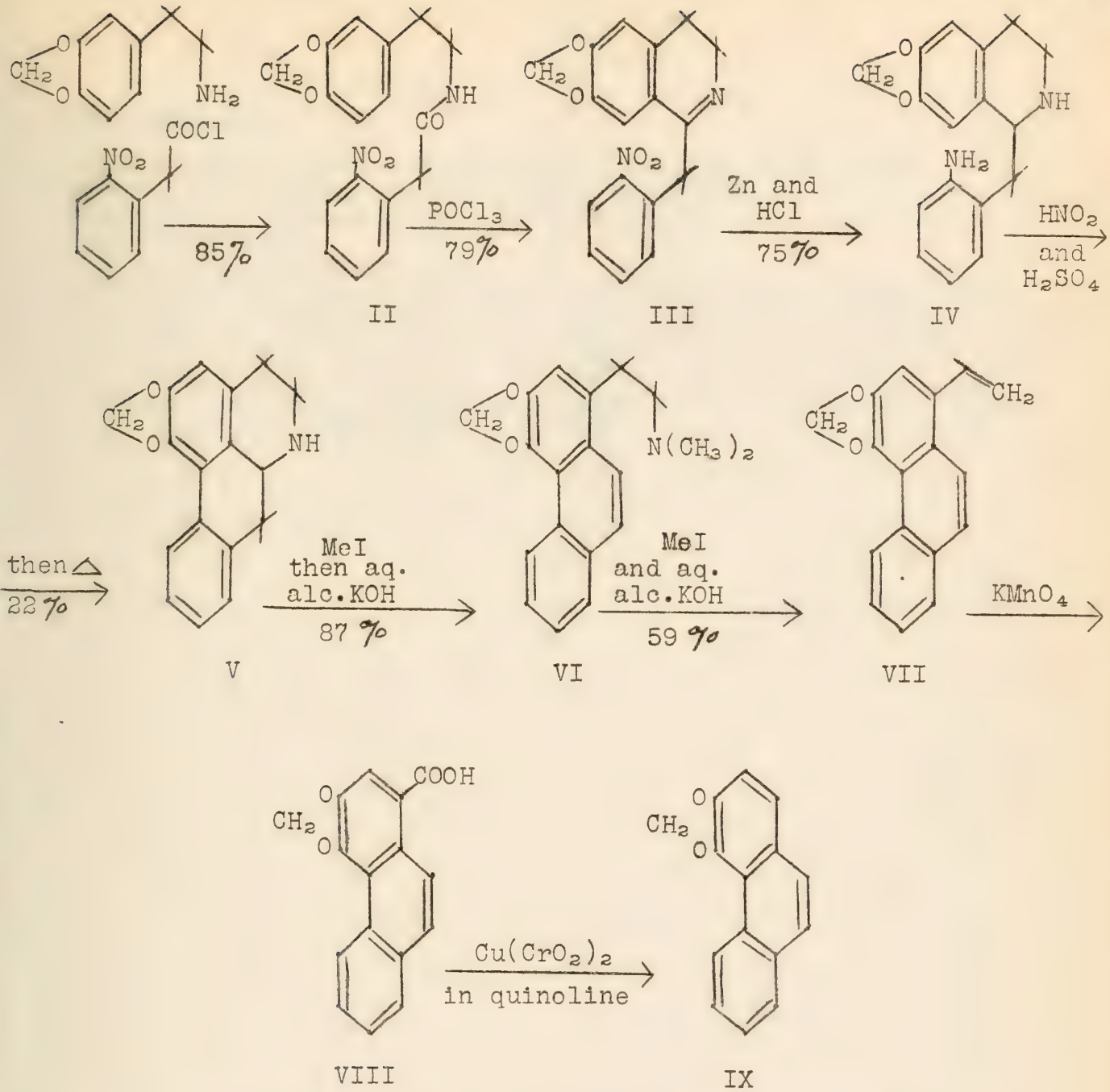
To clinch the structure, an alkaloid of the structure of I was synthesized with the methylenedioxy group in the 5,6-position.

Homopiperonylamine and o-nitrophenylacetyl chloride yielded the amide (II) which was cyclized to the substituted dihydroisoquinoline (III) with phosphorous oxychloride in chloroform. Zinc and hydrochloric acid, as well as reducing the nitro group, reduced the dihydroisoquinoline nucleus to the tetrahydro derivative (IV). Heating of the diazonium sulfate of IV gave dl-anonain (V).

Synthetic dl-anonain gives all the color tests of natural l-anonain, but the synthetic base could not be resolved. However, when natural and synthetic anonain were exhaustively methylated, the first thermal splitting destroyed the asymmetric center; and the products were identical (VI). This identity was preserved all the way to the 5,6-methylenedioxy phenanthrene (IX).

By application of the same degradative and synthetic methods by comparison with degradation products of anonain, the alkaloid roemerine from the plant Roemeria refracta was shown to be N-methyl anonain. Konowalova, Yunoussof, and Orekhoff previously had isolated the alkaloid and established it as an aporphine derivative but had not allocated the position of the methylenedioxy group.





Incidentally, the neatness and dispatch with which this work was carried out was in a large part due to the fact that exactly analogous degradations and syntheses have been used on other aporphine alkaloids, which, as a group, are very closely related; they differ only in combinations of hydroxyl, methoxyl, and methylenedioxy groups on the 2-, 3-, 4-, 5-, and 6-positions. Examples are apomorphine (3,4-dihydroxy-N-methyl-I); boldine (2,6-di-OH-3,5-di-MeO-N-Me-I); glaucine (2,3,5,6-tetra-MeO-N-Me-I); dicentrine (2,3-di-MeO-5,6-methylenedioxy-N-Me-I); laurotetanine (2-OH-3,5,6-tri-MeO-I); actinodaphnine (2-OH-3-MeO-5,6-methylenedioxy-I); corytuberine (4,5-di-OH-3,6-di-MeO-N-Me-I); corydine (5-OH-3,4,6-tri-Meo-N-Me-I); isocorydine (4-OH-3,5,6-tri-MeO-N-Me-I); bulbocapnine (4-OH-3-MeO-5,6-methylenedioxy-N-Me-I).

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Santos, Philippine, J. Sci., 43, 561 (1930)
Konowalova, Yunoussof, and Orekhoff, Bull. soc. chim., Ser. 5, 6, 811 (1939)
Other aporphine alkaloids:
Spath et al., Ber., 60, 1882 (1927); 61, 1692, 2395 (1928); 62, 325 (1929); 64, 2038 (1931); 66, 583, 904 (1933)
Barger et al., J. Chem. Soc., 1928, 2919; Ber., 66, 450 (1933); Helv. Chim. Acta, 14, 481 (1931); 15, 381 (1932)
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Reported by C. M. Smith

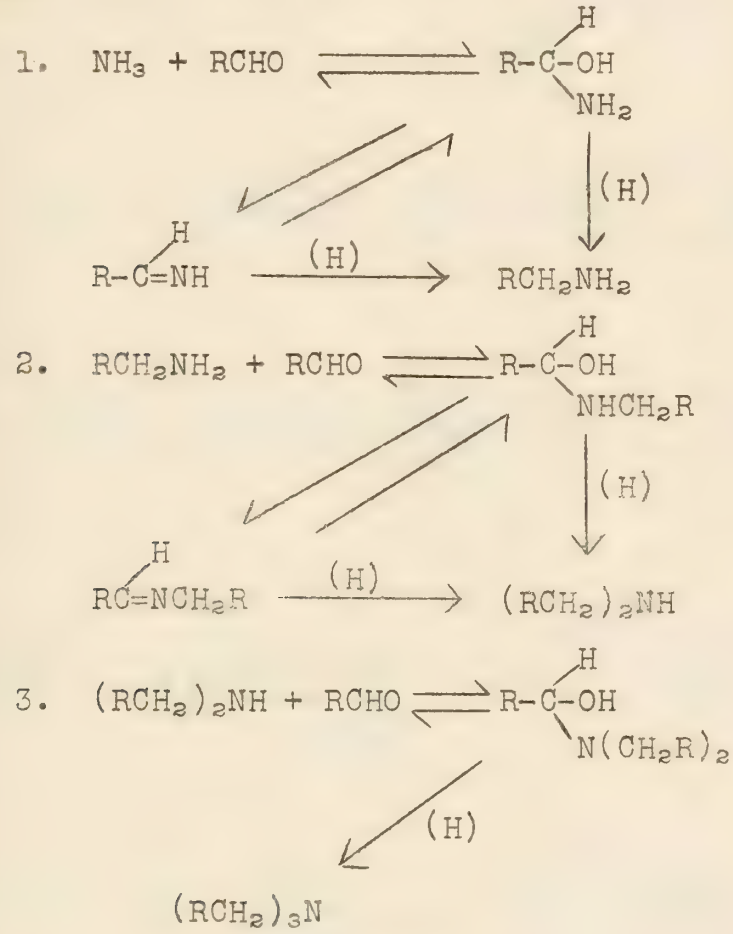
SEMINAR TOPICS

II Semester 1939-40

THE PREPARATION OF AMINES BY REDUCTIVE ALKYLATION

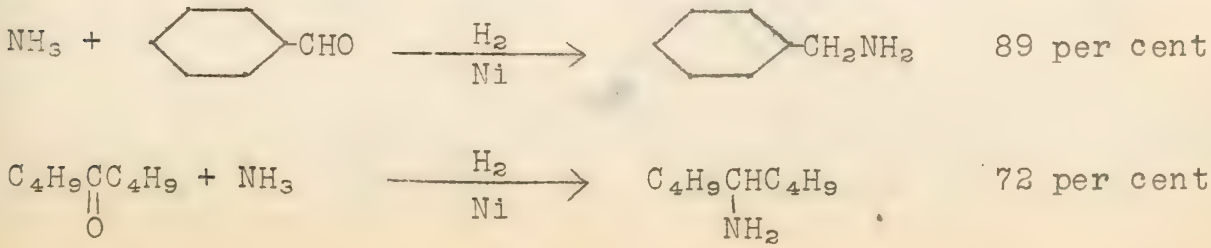
The preparation of amines by reductive alkylation dates back to 1905 when Wallach discovered that amines could be obtained by heating aldehydes or ketones with ammonium formate. Since this initial discovery conditions have been devised for the preparation of primary, secondary, and tertiary amines from aldehydes or ketones and ammonia, primary or secondary amines. A wide variety of reducing agents has been used, the most common being formic acid, zinc and hydrochloric acid, and hydrogen in the presence of platinum, nickel or palladium.

The reaction proceeds according to the following series of equations:

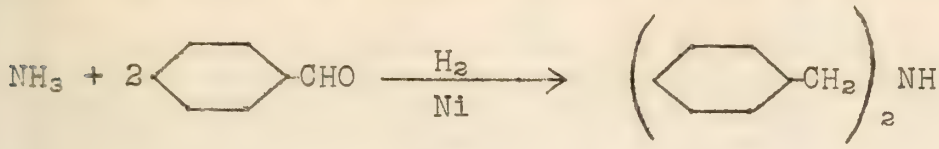


Unless specific conditions are determined in each case, a mixture of amines is the result.

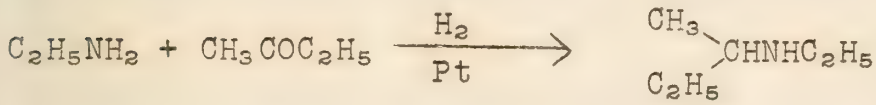
Primary amines are most readily prepared by the reduction of an aldehyde or ketone in the presence of an excess of ammonia.



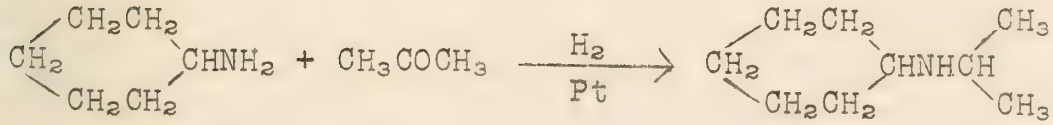
Secondary amines are more difficult to obtain. They are produced most readily in neutral or slightly basic solution from ammonia or more often a primary amine. The best yields are not obtained when both reactants are of low molecular weight.



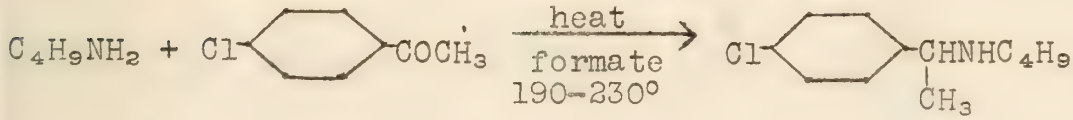
81 per cent



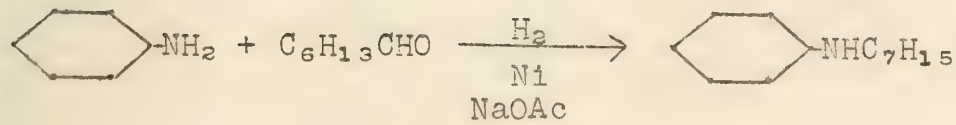
84 per cent



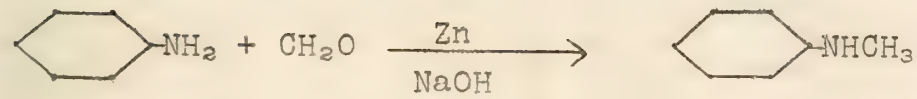
79 per cent



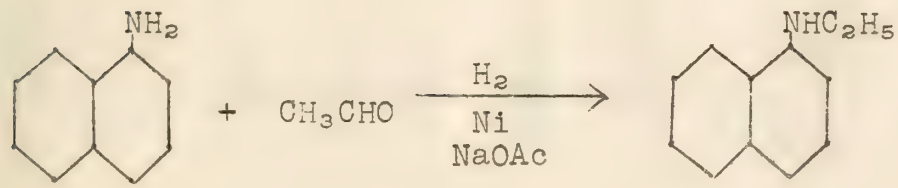
80 per cent



65 per cent

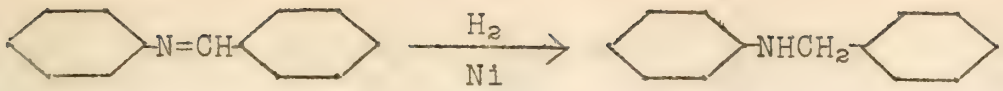


55 per cent



88 per cent

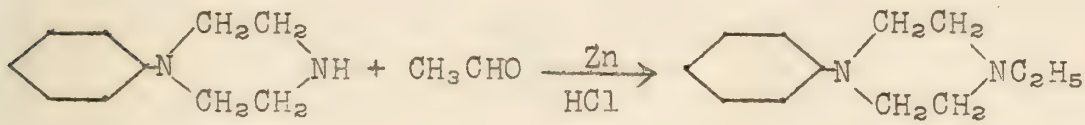
If the intermediate Schiff base is large enough to be stable to hydrolysis, better yields can be obtained by first isolating this intermediate and then reducing it with hydrogen and a catalyst in neutral solution.



97 per cent

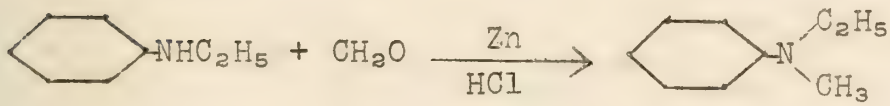
Tertiary amines are obtained by using an excess of aldehyde or ketone with ammonia, a primary or a secondary amine. Acid reducing agents have given the best results. However, this prevents the use of aromatic primary amines since they give polymers when treated with an aldehyde in acid solution.

$$3(CH_2O)_3 + 2NH_4Cl \longrightarrow 2(CH_3)_3N\cdot HCl + 3CO_2 + 3H_2O$$ 89 per cent

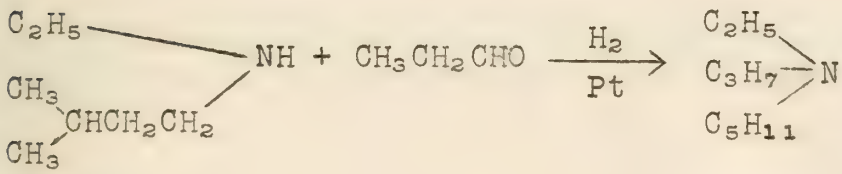


98 per cent

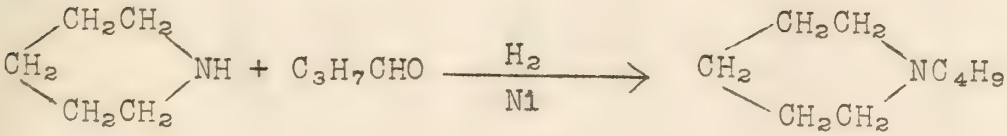
$$H_2N(CH_2)_4NH_2 + 4CH_2O \xrightarrow{H_2CO_2} (CH_3)_2N(CH_2)_4N(CH_3)_2$$ 92 per cent



88 per cent

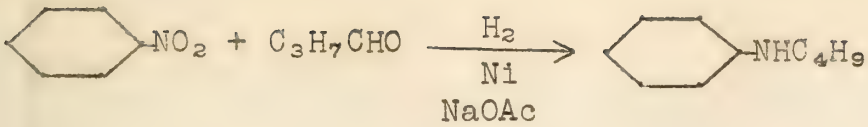


57 per cent



93 per cent

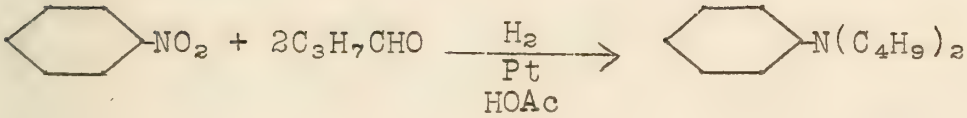
The extension of this reaction to aromatic primary amines has led further to the preparation of secondary and tertiary amines in one step from compounds reducible to primary amines in the reaction mixture.



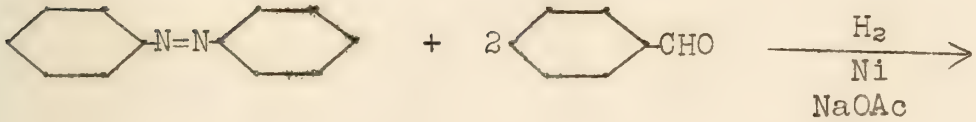
96 per cent

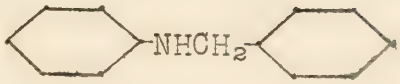
$$CH_3NO_2 + 2CH_3CHO \xrightarrow[\text{Pt, HOAc}]{H_2} CH_3N(C_2H_5)_2$$

92 per cent



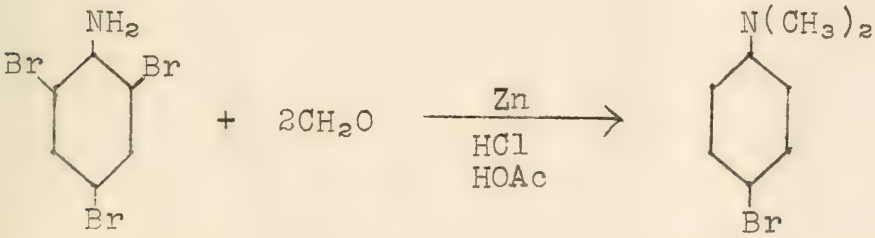
68 per cent





67 per cent

In a study of the reductive alkylation of 2,4,6-tribromoaniline an interesting side reaction occurred as a result of the activation of the bromine atoms by an ammonium salt in the <u>ortho</u>-position.



88 per cent

In conclusion it can be said that reductive alkylation is an excellent method for preparing primary, secondary or tertiary amines from aldehydes or ketones and ammonia, primary or secondary amines, nitro compounds or azo compounds.

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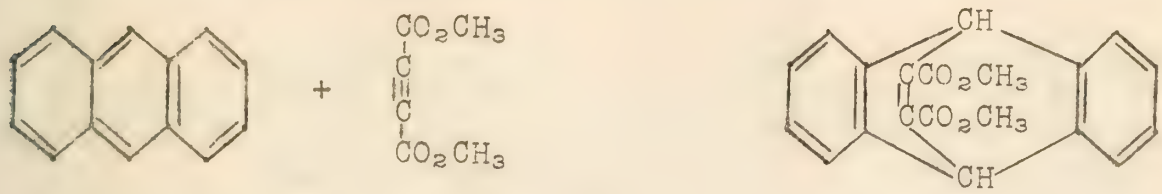
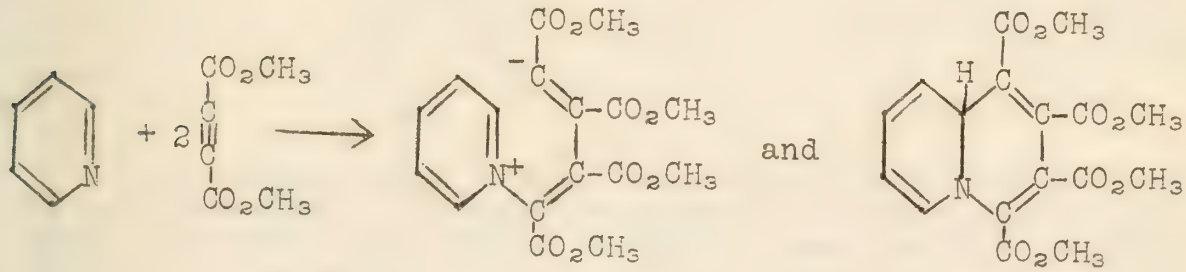
Reported by W. S. Emerson
February 7, 1940.

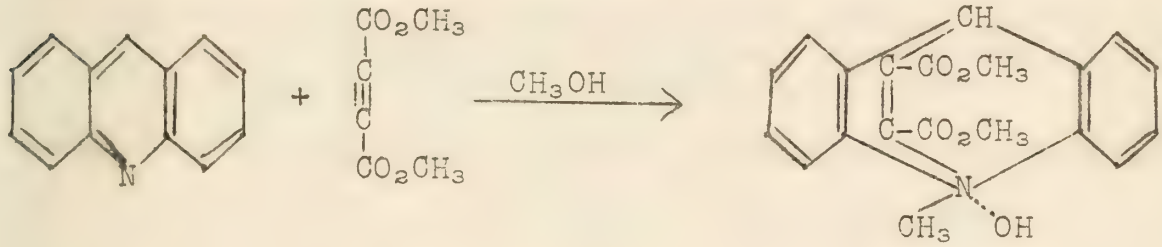
Diels and Thiele recently have investigated the reactions between acridine and methyl acetylene dicarboxylate. Acridine was of peculiar interest because of its relationship both to anthracene and to pyridine, which give radically different reactions.





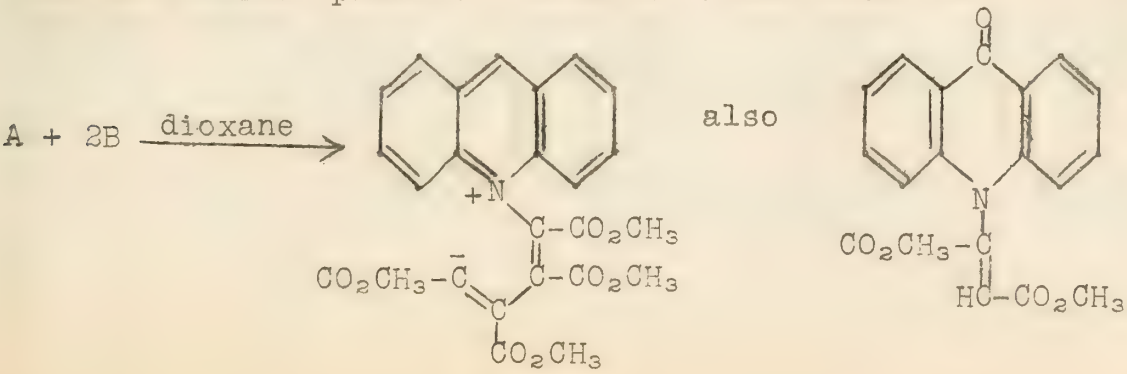
"Labile adduct" "Stable adduct"

In methyl alcohol solution an addition product somewhat similar to those from anthracene was obtained.



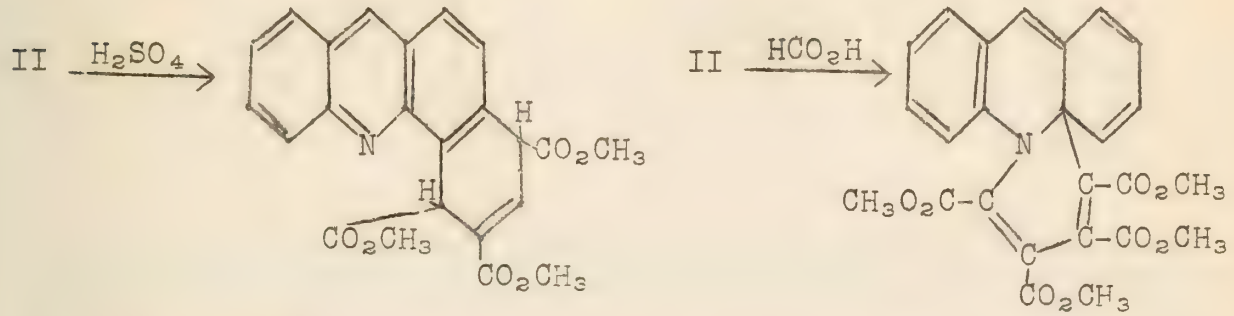
A B I

In dioxane solution, acridine reacted with two molecules of the ester, forming a product (II) related to the labile pyridine adduct. At the same time another substance, apparently derived from an addition product similar to I was obtained.



II III

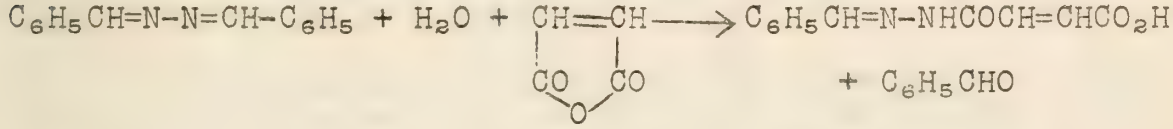
The substance (III), on recrystallization from pyridine, isomerized yielding, presumably, the cis-isomer (IV). The latter also could be obtained by oxidation of I with hydrogen peroxide or air. The labile substance (II) was converted into two stabilization products, depending on whether sulfuric acid or formic acid was used as the reagent.



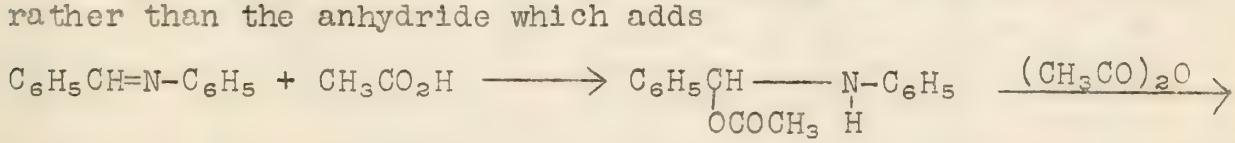
The peculiar reactions of the nitrogen heterocycles have led to a consideration, in this Laboratory, of the behavior of open-chain unsaturates containing nitrogen toward maleic anhydride and acetylene dicarboxylic ester. The reacting pairs chosen were:

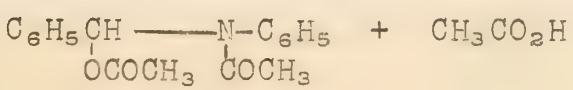
(A) -C=N-N=C- and maleic anhydride
(B) -C=C-C=N- and maleic anhydride
(C) -C=N- and methyl acetylene dicarboxylate, and
(D) -C=C-C=N- and methyl acetylene dicarboxylate

(A) Benzalazine and maleic anhydride failed to give a product of addition or condensation. Unless moisture was excluded the following reaction occurred. Similar reactions of

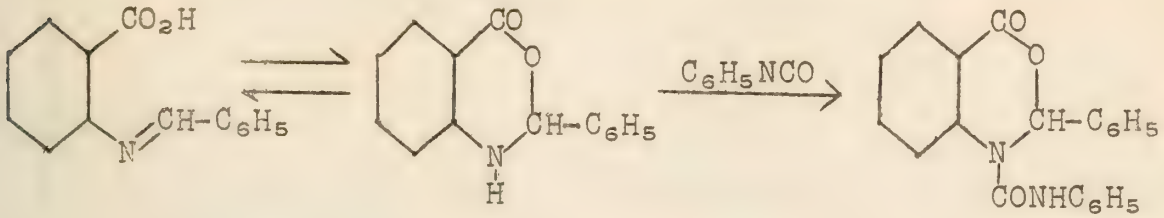


anhydrides on anils and azines have been formulated as involving addition of the anhydride to form compounds containing the grouping $-\underset{COR}{N}-\underset{OCOR}{C}-$ which can be isolated and which are easily hydrolyzed to the amide, aldehyde and acid. Reinvestigation of these reactions showed that the formation of the supposed addition product is catalyzed by traces of acid, indicating that it is the acid rather than the anhydride which adds

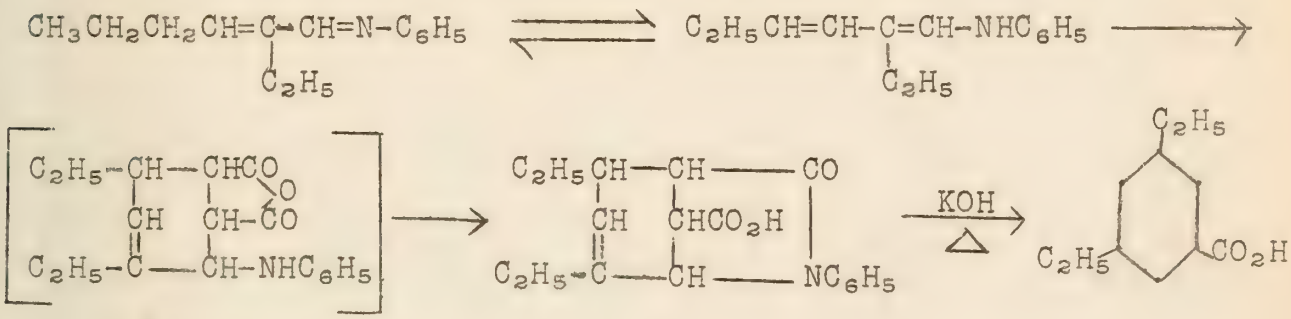




Other evidence supporting this view was found in the cyclization of benzalanthranilic acid, as shown by its reaction with phenylisocyanate as well as by its infrared absorption.



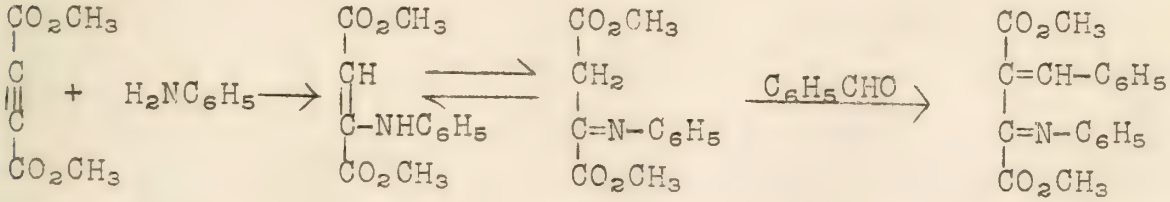
(B) The anil derived from the easily available 2-ethyl-2-hexenaldehyde reacted in its tautomeric form to give a normal diene reaction with maleic anhydride. The product isolated was the



V VI

bicyclic amido acid (VI). The structure was shown by the usual methods of determination of functional groups and by its degradation to diethylbenzoic acid.

(C) Benzalaniline reacted with methyl acetylene dicarboxylate only in the presence of traces of water. The reaction consisted in the hydrolysis of the anil and combination of aniline and benzaldehyde with the ester as shown:



(D) Cinnamalaniline reacted with methyl acetylene dicarboxylate to give two isomeric products whose composition corresponds to one molecule of anil to two of ester. In this respect the reaction resembles that of pyridine. The higher-melting isomer has never been obtained in appreciable yields and it is only recently that the other has been available in amounts large enough to justify structural studies. The failure of α-methylcinnamalaniline, $C_6H_5CH{=}C(CH_3){-}CH{=}N{-}C_6H_5$, to give similar products suggests that the

reaction involves the hydrogen on the α-carbon. It is possible to write formulas for both isomers on this basis, but these have not yet been verified by experiment.

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Reported by H. R. Snyder
February 7, 1940.

THE WORK OF KRÖHNKE ON ENOLBETAINES AND RELATED COMPOUNDS

Kröhnke et al. -- University of Berlin

Intramolecular salts or "zwitterions" formed by compounds containing a quaternary ammonium hydroxide grouping and a carboxyl group in the same molecule are called betaines (see formula I). The formation of betaines is not, however, limited to molecules containing a carboxyl group since other acidic groups have been found to behave similarly. Thus, Benary in 1908 obtained an enolbetaine (II) from the reaction between trimethylamine and chloroacetylcyanoacetic ester in which an enolic group was the acidic portion of the molecule.

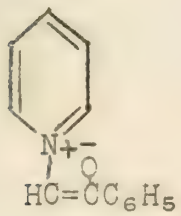
$$(CH_3)_3\overset{+}{N}CH_2\overset{-}{COO} \qquad\qquad (CH_3)_3\overset{+}{N}CH_2\overset{-}{C}O{=}C(CN)COOC_2H_5$$

I II

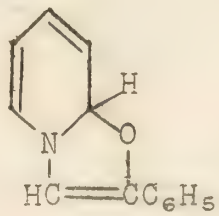
Kröhnke in 1933 in studying the degradation of phenacyl halides by alkali in the presence of pyridine noted the formation of an intermediate unstable yellow oil. Further work on the reaction between phenacylpyridinium salts and milder alkalies such as sodium or potassium carbonates resulted in the isolation of a crystalline solid which, on treatment with acids, was converted again into the corresponding phenacylpyridinium salt:

$$\left[C_6H_5COCH_2\overset{+}{N}C_5H_5\right]Br^- \underset{HBr}{\overset{K_2CO_3}{\rightleftharpoons}} C_6H_5\overset{-}{C}O{=}\overset{+}{C}HNC_5H_5$$

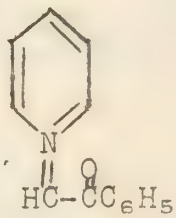
Although structures III, IV, and V may be written for this compound, the enolbetaine (formula III) has been assumed to be correct since it adequately accounts for the intense color of these substances and also agrees with their chemical behavior.



III

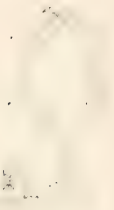


IV



V

Enolbetaines are crystalline compounds which are soluble in most organic solvents and are unstable in air. They can, however, be kept practically unchanged in a vacuum over phosphorus pentoxide. They liberate ammonia from ammonium salts and tend to form molecular compounds.



In chemical behavior, enolbetaines are similar to 1,3-diketones. Thus, on acylation with acid anhydrides or acyl halides, the C-acyl derivative (VI) is obtained in most cases:

$$C_6H_5\overset{-}{C}O{=}CH\overset{+}{N}C_5H_5 \longrightarrow C_6H_5\overset{-}{C}O{=}C(COR)\overset{+}{N}C_5H_5$$

VI

Pyridinium enolbetaines liberate one mole of methane on treatment with methylmagnesium iodide (Zerewitinoff determination) and react with phenylisocyanate and with benzene diazonium chloride resulting in a substitution of the methine (=CH-) hydrogen:

$$R\overset{-}{C}O{=}CH\overset{+}{N}C_5H_5 \xrightarrow{C_6H_5NCO} R\overset{-}{C}O{=}\underset{\underset{CONHC_6H_5}{|}}{C}\overset{+}{N}C_5H_5$$

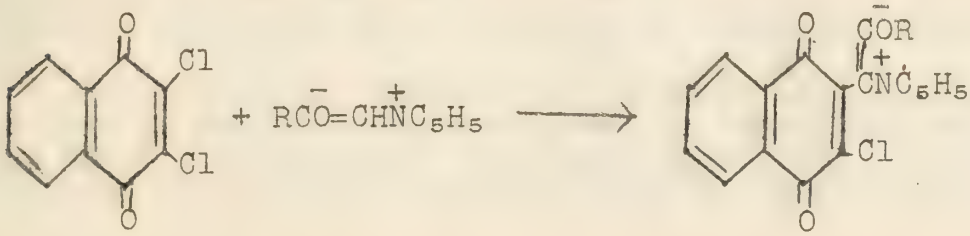
$$\xrightarrow{C_6H_5N_2Cl} R\overset{-}{C}O{=}\underset{\underset{N{=}NC_6H_5}{|}}{C}\overset{+}{N}C_5H_5$$

Enolbetaines react readily with aryl nitroso compounds giving a nitrone (VII). Although the true course of the reaction is not known, the probable mechanism of the reaction is represented:

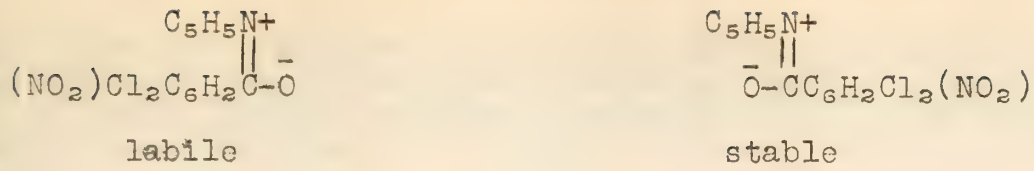
$$R\overset{-}{C}O{=}CH\overset{+}{N}C_5H_5 \xrightarrow{ArNO} R\overset{-}{C}O{=}\underset{\underset{ArNOH}{|}}{C}\overset{+}{N}C_5H_5 \longrightarrow R\underset{\underset{ArNOH}{|}}{C}OCHOH \longrightarrow R\underset{\underset{O}{\downarrow}}{C}OCH{=}NAr$$

VII

Concentrations of enolbetaines as low as 1 part in 200,000 give intense color reactions with picryl chloride and also with quinones. The result of the reaction with picryl chloride is analogous to that obtained with ordinary acyl halides. In the case of the quinones, the enolbetaine behaves as a metallic enolate of a 1,3-diketone:

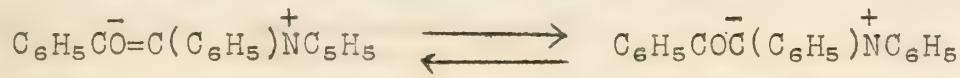


Isomeric compounds which Kröhnke believes are the <u>cis</u>-<u>trans</u>-isomers (VIII and IX) have been isolated in the case of 2-nitro-3,4-dichlorophenacylpyridinium enolbetaine.



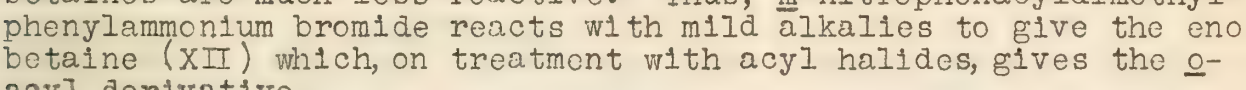
labile VIII stable IX

Enolbetaines having no active hydrogen (see formula X), although showing none of the reactions involving the methine hydrogen in alkaline solution in the above cases, react smoothly with aryl nitroso compounds in a manner similar to that of diazomethanes. On this basis, a mesomerism between a carbeniate zwitterion (XI) and the enolbetaine has been postulated.



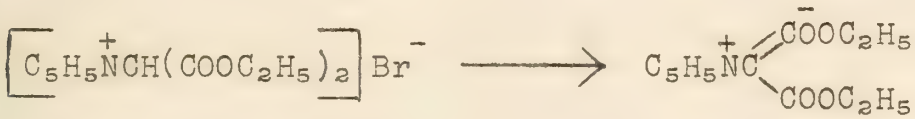
X XI

Quinolinium and isoquinolinium enolbetaines are formed also in accord with the above reactions. Tertiary amines other than cyclic also have been used but in these cases the resulting enolbetaines are much less reactive. Thus, m-nitrophenacyldimethylphenylammonium bromide reacts with mild alkalies to give the enolbetaine (XII) which, on treatment with acyl halides, gives the o-acyl derivative.



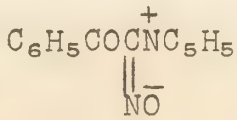
XII

The reaction between the pyridinium salt obtained from bromomalonic ester and pyridine and alkalies (K_2CO_3) gives a new type of enolbetaine in which the enolate of the malonic ester residue is the anionic portion of the zwitterion.



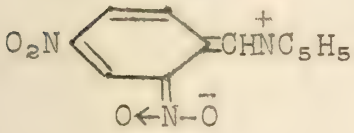
This is the first reported case of an enolate of malonic ester in which the enolic group is attached to other than a metal cation.

More recently, Kröhnke has isolated several other types of betaines in which the anionic group is other than enol. Thus, when ethyl nitrite reacts with phenacylpyridinium bromide in alkaline solution, the isonitrosobetaine (XIII) is obtained.

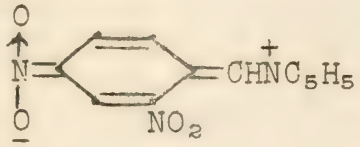


XIII

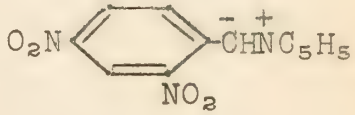
A highly colored acinitrobetaine which Kröhnke believes may be an equilibrium of the various resonance forms (XIVa, b, and c) has been obtained from the reaction between 2,4-dinitrobenzylpyridinium chloride and alkalies.



XIVa

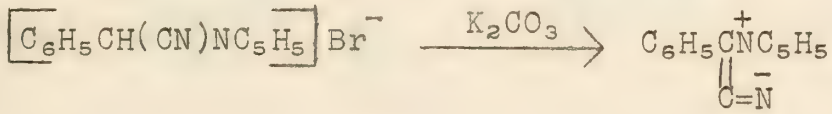


XIVb



XIVc

A fifth type of betaine (emininebetaine) has been obtained from α-cyanobenzylpyridinium bromide:



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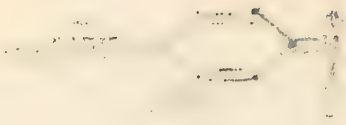
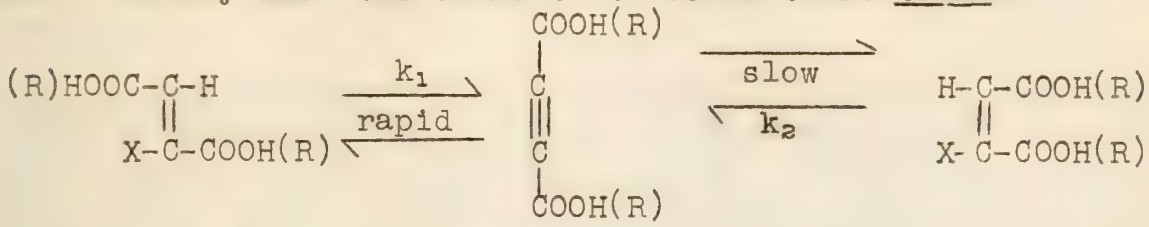
Kröhnke, ibid., 66, 604 (1933); 68, 1177 (1935); 70, 543, 1114 (1937); 72, 83, 527 (1939).
Kröhnke and Kübler, ibid., 70, 538, 1117 (1937).
Kröhnke and Börner, ibid., 69, 2006 (1936).
Kröhnke and Schmeiss, ibid., 70, 1728 (1937); 72, 440 (1939).
Kröhnke and Heffe, ibid., 70, 1720 (1937).

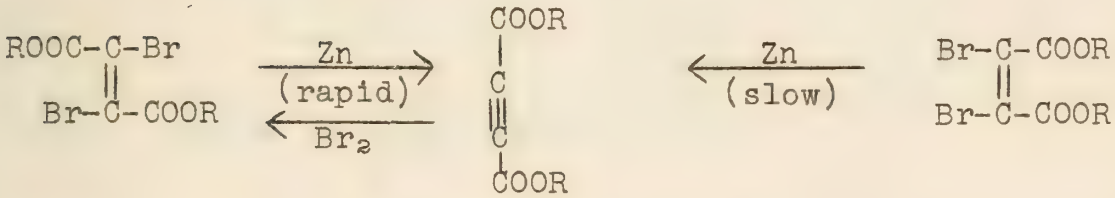
Reported by E. W. Kaiser
February 14, 1940.



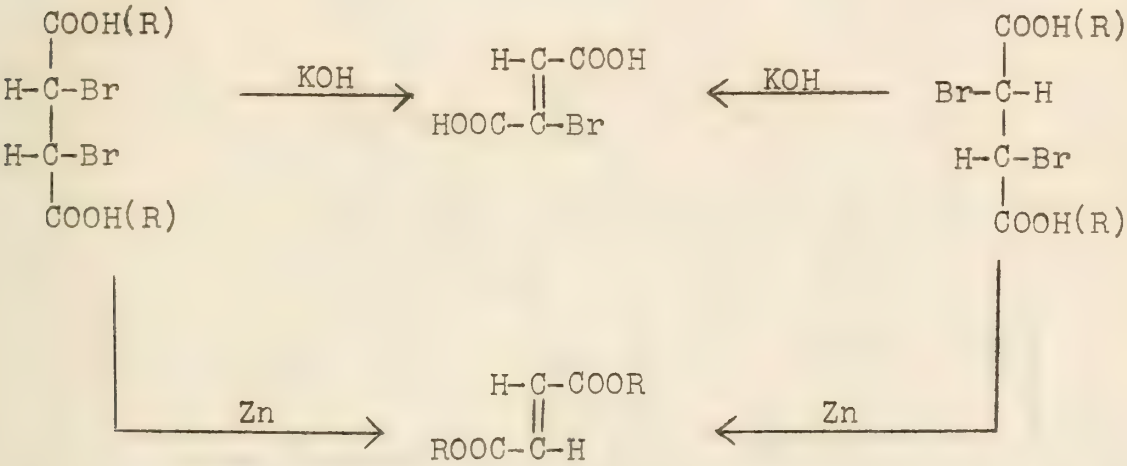
Researches of Michael, Chavanne, and van der Walle have shown that elimination reactions to establish a triple bond take place most readily when the elements to be lost are <u>trans</u>.



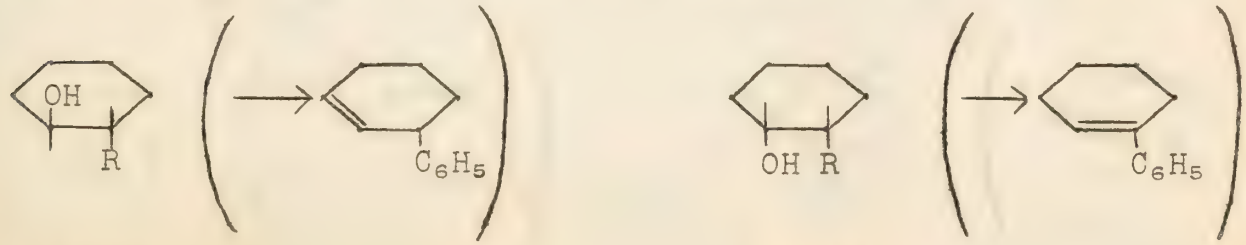
(for X = Br, k_1/k_2 = 50; for X = Cl, k_1/k_2 = 15)



Similar studies by Michael on elimination involving saturated carbon atoms showed no such consistent results, the more stable <u>trans</u>-form usually resulting from both <u>meso</u>-and <u>racemic</u>-type isomers.



Vavon and Barbier found that <u>cis</u>-<u>o</u>-alkyl cyclohexanols eliminate water more readily than the <u>trans</u>-isomers, corresponding to easy <u>trans</u>-elimination. They did not determine the structure of

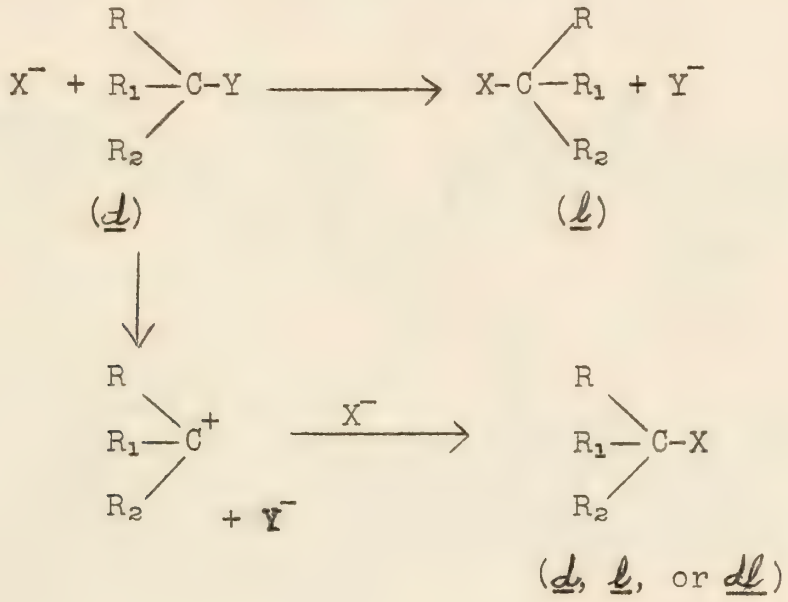


I (<u>trans</u>) II (<u>cis</u>)

the olefins formed. Huckel and Neunhoeffer found that with R = cyclohexyl, II gave Δ^1-cyclohexyl cyclohexene easily while I gave this olefin less readily plus an isomer, Δ^1-hexahydrobenzylcyclopentene.

With R = phenyl, II gave Δ^1-phenylcyclohexene while I gave Δ^2-phenylcyclohexene, a case in which trans-elimination takes place even to give a less stable isomer. The trans-alcohol in this case has been prepared by reduction of 2-phenylcyclohexanone with sodium in alcohol or from cyclohexene oxide and phenyllithium. The cis-isomer results from the catalytic hydrogenation of o-phenylphenol.

Halogenation.--Although a great deal of work has been done on the stereochemistry of substitution at a saturated carbon atom since Walden discovered that inversion of configuration may occur in such reactions, these have all involved replacement of one negative group by another (OH, Cl, Br, I, NH_2) by reactions proceeding through an ionic mechanism.

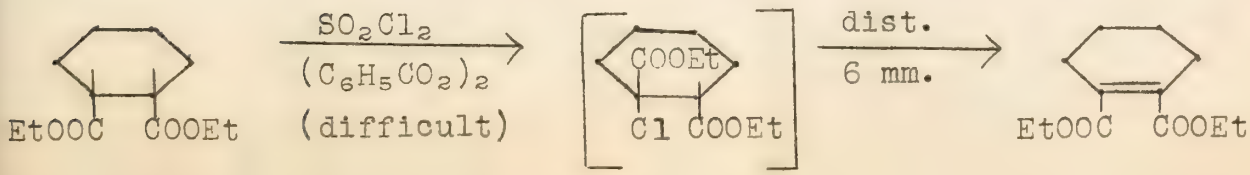


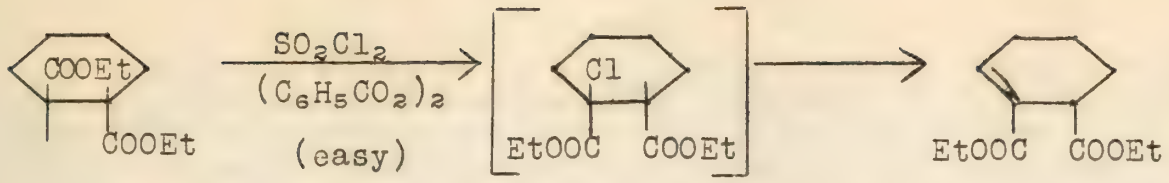
In order to make such a study for halogenation, in which a hydrogen is replaced by halogen through an atomic mechanism, the chlorination of cis- and trans-diethylhexahydrophthalates using sulfuryl chloride with peroxide catalysis has been studied.

$$\text{peroxide} \longrightarrow R^*$$

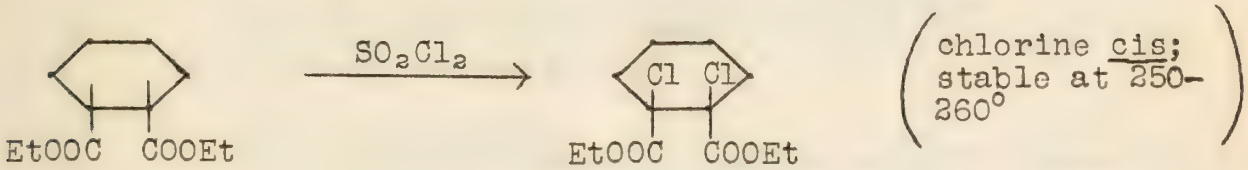
$$R^* + SO_2Cl_2 \longrightarrow RCl + SO_2Cl^*$$

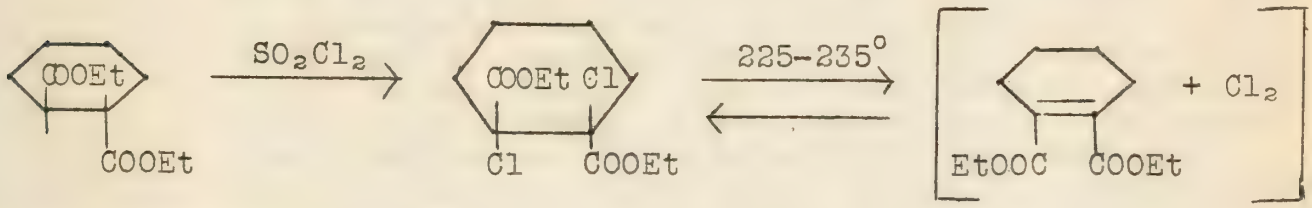
$$SO_2Cl^* \longrightarrow SO_2 + Cl^*$$





Using an excess of sulfuryl chloride, the cis-ester gave a product which did not distil at 250-260°(6 mm.). From the trans-ester, the material did not distil until the bath reached 225-235° but it boiled at the same temperature as the unsaturated ester (150° (6 mm.)). It had a fleeting yellow color and analyzed just a little low for the dichloro ester.





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Reported by C. C. Price
February 14, 1940.

ALKYLATION, CYCLO-ALKYLATION, AND CYCLI-ALKYLATION OF AROMATIC COMPOUNDS

The introduction of an alkyl group into an aromatic ring by the condensation of a monofunctional aliphatic hydrocarbon derivative with an aromatic compound is known as alkylation. If a cyclic aliphatic hydrocarbon is introduced into the aromatic nucleus, the process is known as cyclo-alkylation. Cycli-alkylation occurs when a suitable difunctional aliphatic hydrocarbon derivative condenses with the aromatic ring at the two points on the difunctionally reactive open chain to form a new cycle resulting in a hydroaromatic compound.

Alkylation of Aromatic Compounds.--

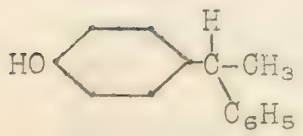
1. Use of halogenated aliphatic compounds.
   The Friedel-Crafts reaction is employed for this type of alkylation.

2. Use of alcohols.
   Boron trifluoride and aluminum chloride cause the condensation of alcohols with aromatic hydrocarbons and derivatives to give alkylated aromatic compounds. Primary alcohols, particularly the lower members, give no appreciable reaction. Secondary alcohols give only fair yields. Tertiary alcohols readily condense with good yields. Benzene, naphthalene, phenols, and their chloro derivatives have been alkylated in this manner. Boron trifluoride gives chiefly the para-compound. Aluminum chloride gives either the meta- or para-compound or both depending on the type of aromatic compound being alkylated. Mono-, di-, or polyalkylated derivatives are obtained depending on the amount of catalyst and the temperature employed.

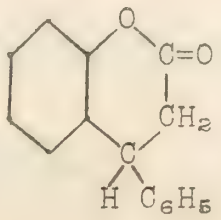
   Examples: Phenol and t-amyl or t-butyl alcohol with aluminum chloride gives the para-alkyl phenol. Naphthalene and t-butyl alcohol using boron trifluoride as the catalyst gives chiefly β-t-butyl naphthalene.

3. Use of unsaturated compounds.
   Isoamylene and styrene condense with phenol in the presence of sulfuric acid and acetic acid to give p-isoamyl phenol and 1,1-p-hydroxyphenylphenyl ethane (I).

   Cinnamic acid condenses with phenol to give phenylhydrocoumarin (II).



I



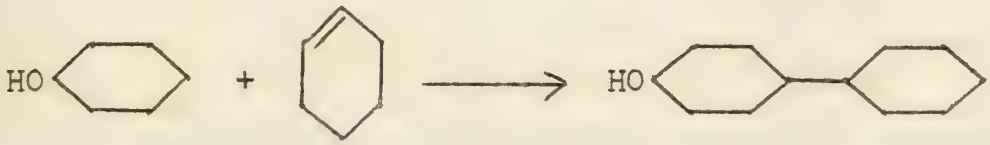
II

Other phenols also react to give substituted phenylhydrocoumarins.

4. Use of esters.
Benzene can be alkylated with esters using boron trifluoride. The yields are proportional to the amount of catalyst used. Ethyl formate, isopropyl formate, isobutyl formate yield ethyl, isopropyl, t-butyl benzene, respectively. Considerable di- and polyalkyl benzenes are formed also. Aluminum chloride gives good results where boron trifluoride fails.

Cyclo-alkylation of Aromatic Compounds.--

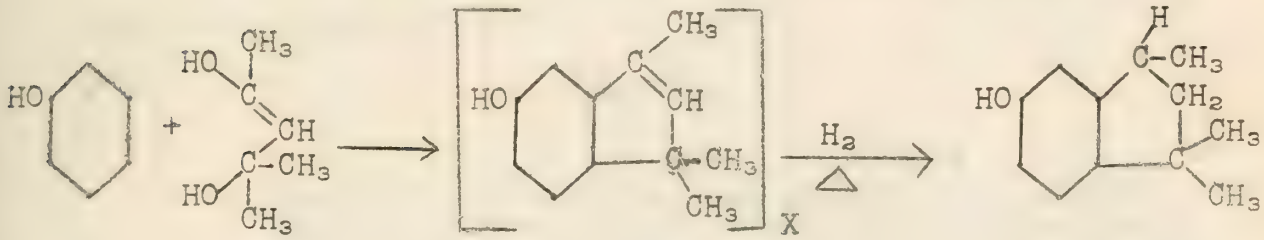
This reaction involves the introduction of a monovalent cyclo-aliphatic group, such as cyclohexyl, cyclopentyl, etc., into an aromatic nucleus. Cyclohexene, the methyl cyclohexenes, 1,3-dimethyl cyclohexene-5, octahydronaphthalene, dihydronaphthalene condense with phenol in the presence of sulfuric acid and acetic acid to form cyclo-alkylated phenols.



Cyclohexanol condenses with benzene to give mono- and dicyclohexyl derivatives.

Cyclo-alkylation of Aromatic Compounds.--

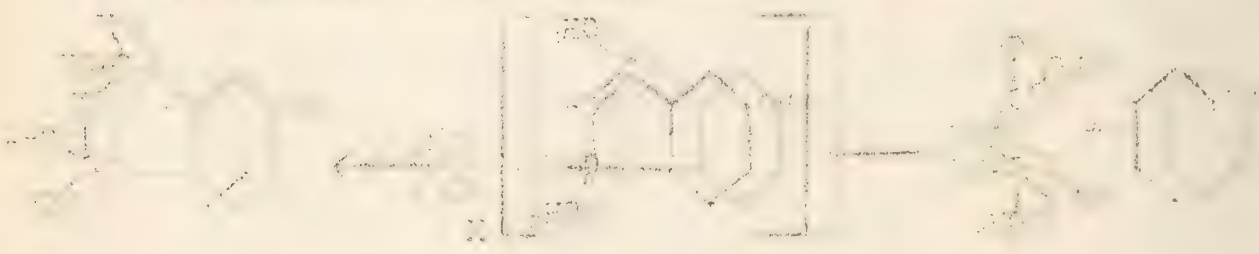
1. Alkylated phenolic hydroxy indenes and indanes.
Diacetone alcohol and pinacol condense with phenols by refluxing with zinc chloride. A polymer is obtained in the case of diacetone alcohol. Pyrolysis of this polymer yields small amounts of 1,3,3-trimethyl-6-hydroxyindane (III); yield 10-15 per cent.

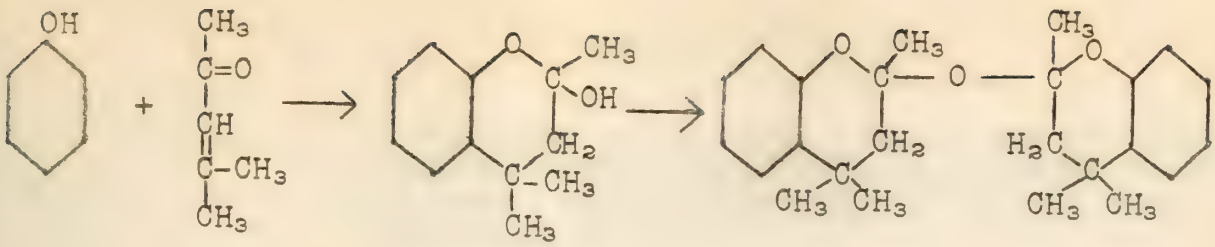


III

Pinacol yields 1,1,2-trimethyl-5-hydroxyindane upon condensing with phenol.

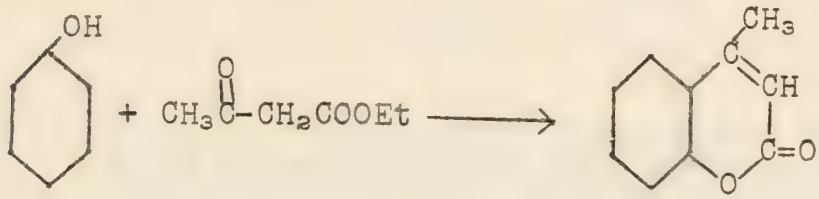
2. Chromanols and dichromanyl ethers.
Monohydroxy benzene derivatives are condensed with mesityl oxide by means of sulfuric acid. Phenol yields chromanol (IV) and dichromanyl ether (V).





IV V

3. Courmarins.
β-Ketonic esters condense with phenols in the presence of aluminum chloride to give coumarin derivatives. Phenol and acetoacetic ester give 4-methyl coumarin (VI); yield 30-40 per cent.



VI

Methyl β-resorcylate with acetoacetic ester gives good yields 5-hydroxy-4-methylcoumarin-6-carboxylate.

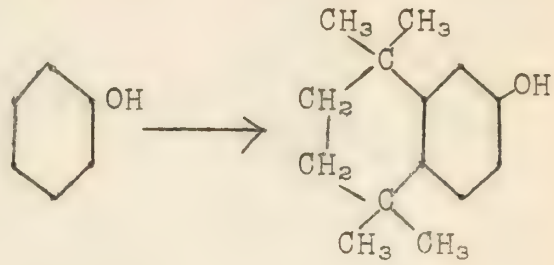
4. Hydroaromatic compounds from tertiary 1,4-glycols, chlorides, and 1,5-diolefins.

(a) Reactions with phenols and aluminum chloride.

$(CH_3)_2C(OH)CH_2CH_2(OH)C(CH_3)_2$

$(CH_3)_2(Cl)CH_2CH_2(Cl)C(CH_3)_2$ +

$CH_2=C(CH_3)CH_2CH_2(CH_3)C=CH_2$



X

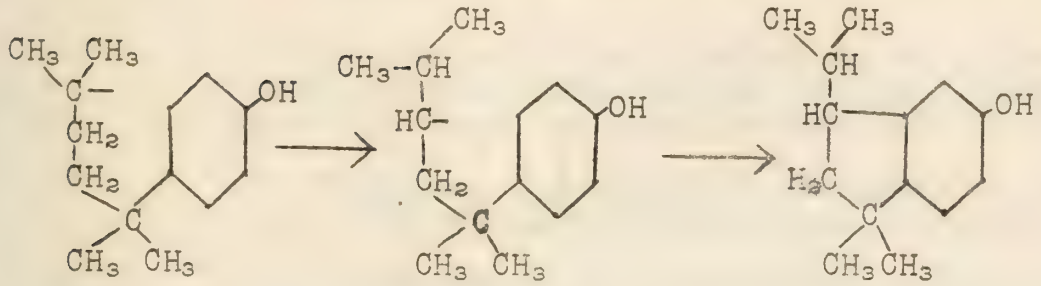
Phenols used to give compounds of type X were: phenol, o-cresol, m-cresol, 2,6-dimethyl phenol, pyrocatechol, o-phenylphenol, o-cyclohexylphenol, and o-chlorophenol.

Phenols which are blocked in the para-position yet open in the ortho-position, for example, p-cresol, give chromanes or coumaranes.

(b) Reactions with sulfuric acid and boron trifluoride.

If aluminum chloride is replaced by boron

trifluoride or sulfuric acid in the previous condensations, a hydroxyindane derivative (XI) is formed by the rearrangement of the cycli-alkylating group.

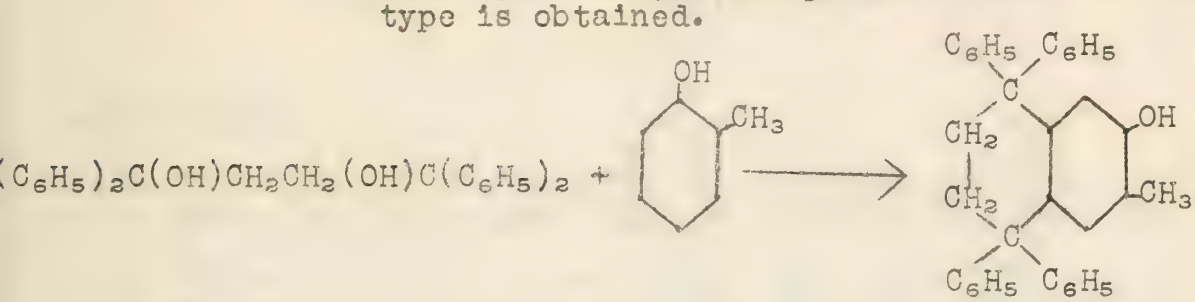


XI

Boron trifluoride at 0° C has little tendency to cause rearrangement so that normal derivatives (X) identical with those obtained from aluminum chloride result.

(c) Other cycli-alkylation reactions.

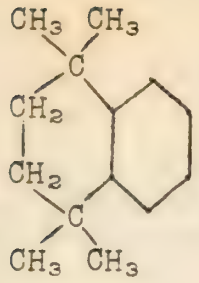
1,1,4,4-Tetraphenylbutan-1,4-diol (XII) gives no appreciable condensation with phenol or o-chlorophenol. With o-cresol a definite crystalline cycli-alkylation product (XIII) of the usual type is obtained.

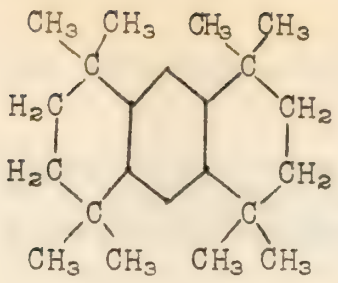


XIII

Secondary aliphatic 1,4-glycols also condense with phenol in the presence of 77 per cent sulfuric acid to cycli-alkylate the aromatic nucleus. The primary aliphatic 1,4-glycol, 1,4-dihydroxybutane, will not condense with phenol.

5. Cycli-alkylation using 2,5-dichloro-2,5-dimethyl hexane (VIII).
VIII and benzene in the presence of aluminum chloride gives both mono- and dicycli-alkylation products.





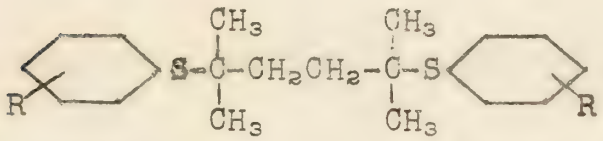
Catalytic quantities of aluminum chloride yields mostly monocycli-alkylation product, while large amounts favor the dicycli-alkylation product.

Toluene, o-chlorotoluene, tetralin, and hydrindene give similar monocycli-alkylation products.

Naphthalene and diphenylene oxide give the dicycli-product, the latter yielding in addition some of the monocycli-product.

Thiophene with stannic chloride gives only the monocycli-alkylated product.

6. Condensations with thiophenols.
Compounds VIII and IX instead of undergoing cycli-alkylation with thiophenols form dithio ethers.



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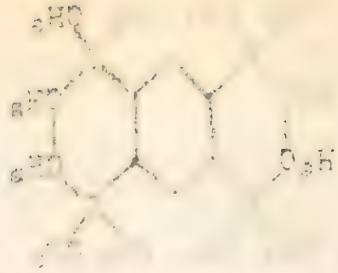
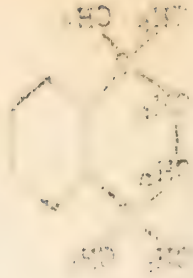
Reported by L. A. Patterson
February 21, 1940.

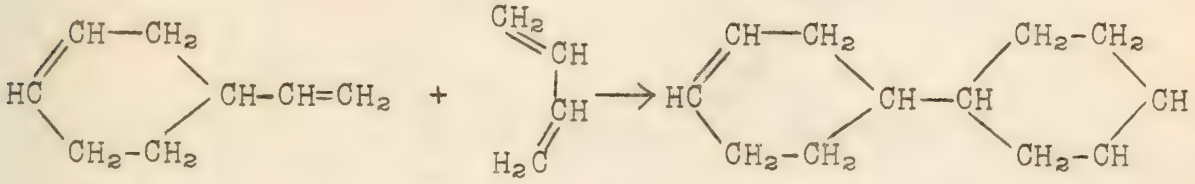




RECENT DEVELOPMENTS IN THE DIENE SYNTHESIS

Kurt Alder -- I. G. Farbenindustrie

In the early part of 1938 Alder discovered that vinylcyclohexene would add one molecule of 1,3-butadiene according to the normal diene reaction to form a partially hydrogenated biphenyl.



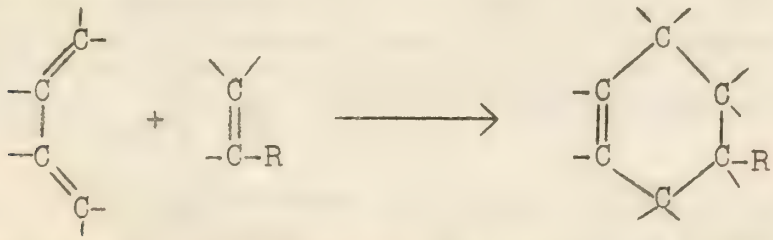
Prior to this time it was believed that 1,3-dienes would undergo the Diels-Alder reaction only with conjugated unsaturated compounds of the following general types:

1. The best known group has the >C=C< attached to a polar group like >C=O, -C≡N, or -N(→O)=O. These also give better yields, faster reactions, and can be condensed at lower temperatures. Examples: acrolein, maleic anhydride, quinone, and acrylonitrile.

2. Conjugated compounds which do not contain polar groups.

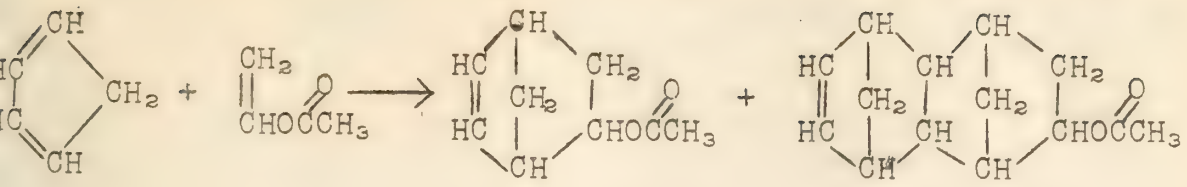
   Examples: >C=C-C=C< and >C=C- 

The above reaction was the first instance of a Diels-Alder reaction with a compound not included in the general types listed. Further study showed that compounds of the following types readily undergo a normal Diels-Alder reaction: vinyl chloride, di- and trichloroethylenes, vinyl acetic acid, vinyl acetates and formates, allyl chloride and allyl cyanide. These add normally to 1,3-cyclopentadiene, butadiene, 2,3-dimethylbutadiene, and 1,3-cyclohexadiene. Usually dimers also are formed. These olefins exhibit no conjugation, but the molecule carries a polar group which may or may not be directly attached to the double bond. A general equation representing the addition of the above types to a diene may be given as follows:



Reactions of this type are of synthetic importance since many types of compounds, hitherto very difficult to prepare, may be obtained in fair yields through this new extension of the diene synthesis.

Preparation of norcamphor:



A
44 per cent

B
28 per cent

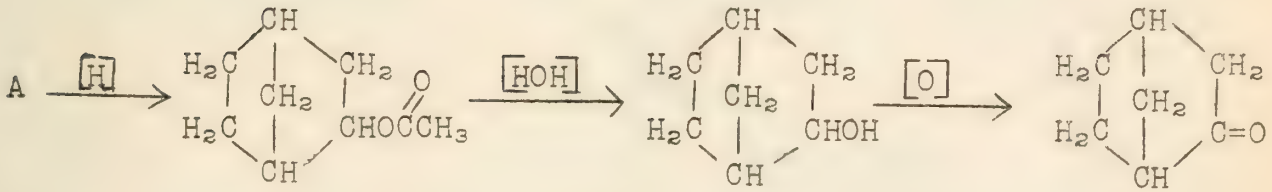


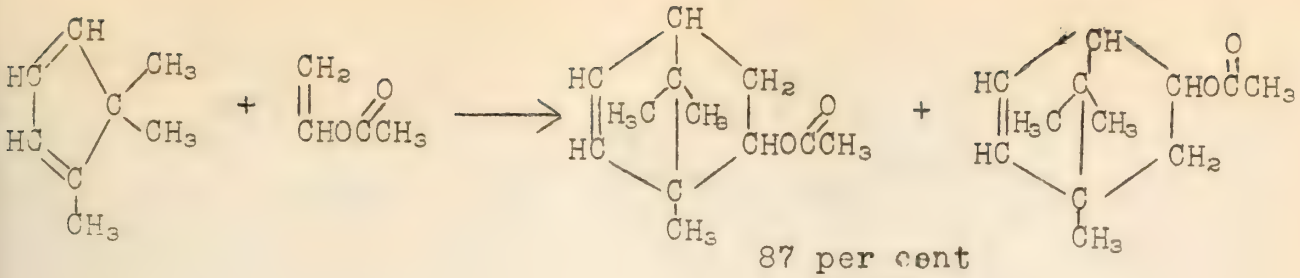
Table I contains some of the representative olefinic compounds and the yields of the monomers and dimers formed by addition to the indicated dienes.

Table I

Diene	Olefin	Per cent Yield of Monomer	Per cent Yield of Dimer
Cyclopentadiene	vinyl acetate	44	28
Cyclopentadiene	vinyl formate	40	32
Butadiene	vinyl acetate	--	--
2,3-Dimethylbutadiene	vinyl acetate	--	--
1,3-Cyclohexadiene	vinyl acetate	--	--
Anthracene	vinyl acetate	10	--
Cyclopentadiene	vinyl chloride	47	24
Cyclopentadiene	dichloroethylene	21	27
Cyclopentadiene	trichloroethylene	--	--

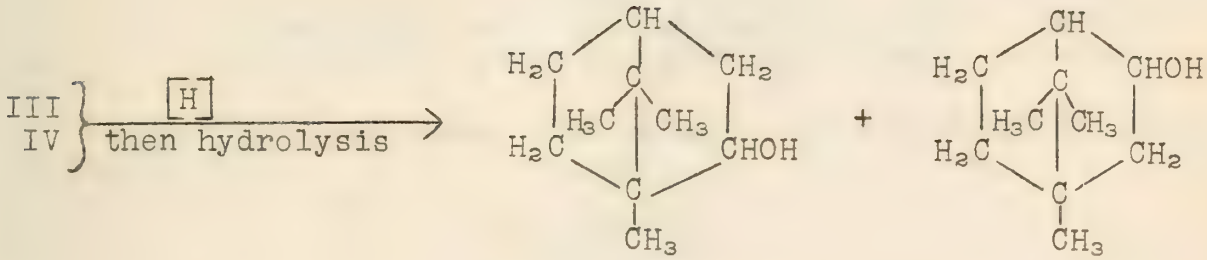
The reaction of vinyl esters with 1,3-dienes affords a good method for producing cyclic alcohols with the -OH attached to the ring. The reactions with cyclopentadiene are interesting since they lead to norcamphor compounds. The number and variety of products are limited only by the number of derivatives of cyclopentadiene. The use of 1,5,5-trimethylcyclopentadiene-1,3 would lead to camphor derivatives.

1. Vinyl acetate (I) adds smoothly to 1,5,5-trimethylcyclopentadiene-1,3 (II) yielding a mixture of dehydroborneol (III) and dehydroepiborneol acetates (IV). Reduction and hydrolysis of the mixture yields a mixture of the alcohols. These alcohols may be oxidized to the corresponding camphors or reduced to camphanes.



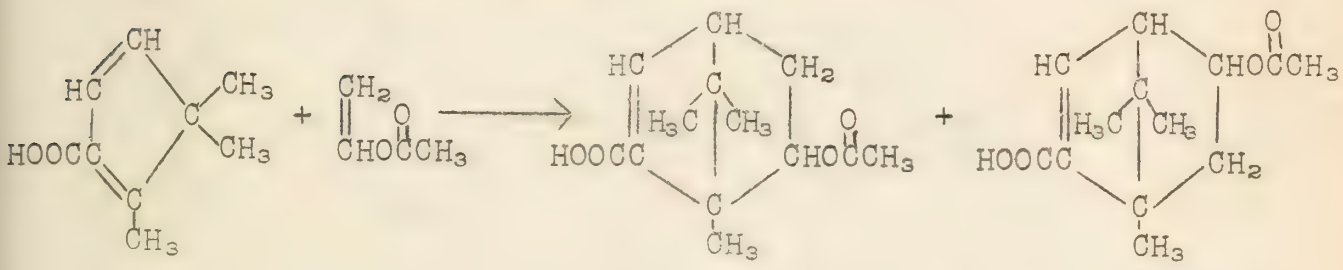
87 per cent yield

II I III IV



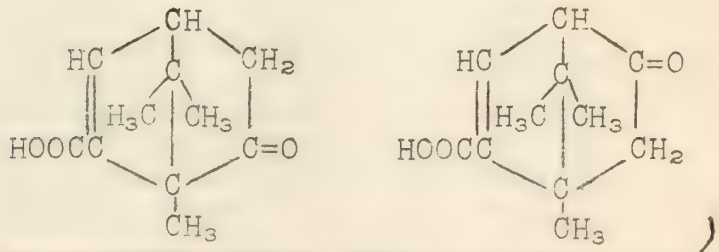
97 per cent yield

2. Vinyl acetate adds to β-camphylic acid yielding a mixture of products. The following reactions establish the course of the diene synthesis.

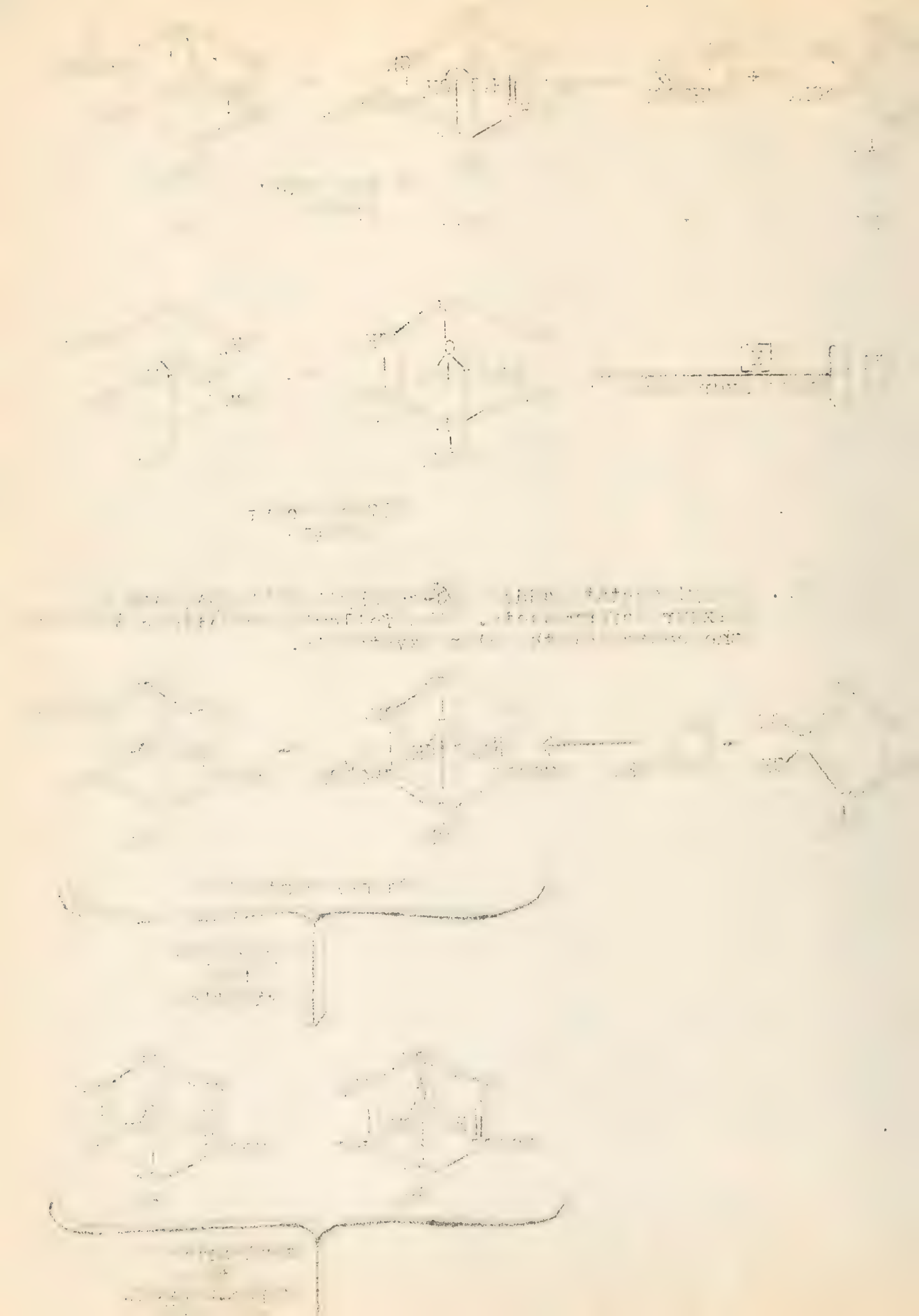


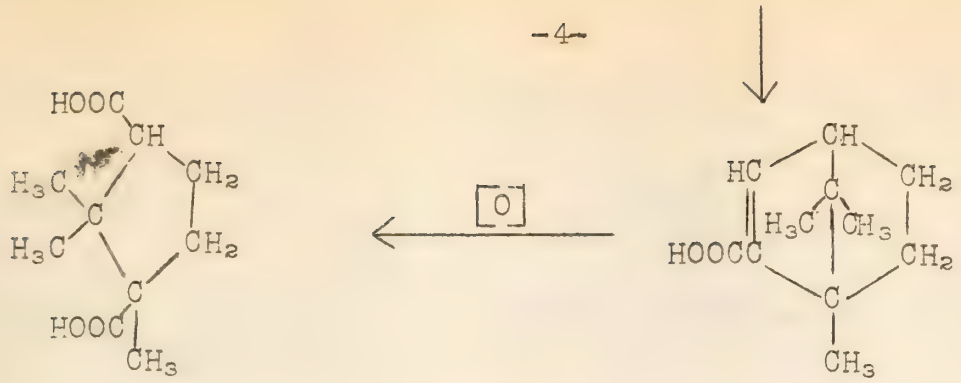
84 per cent yield

hydrolysis then oxidation



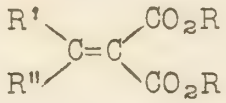
semicarbazone then Wolff-Kishner reduction



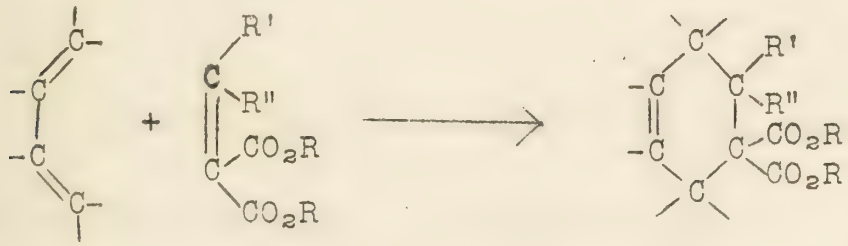


3. 1,5,5-Trimethylcyclopentadiene-1,3 adds to acetylenedicarboxylic acid or its dimethyl ester. In both cases the addition follows the expected course.

Recent work has shown that malonic ester derivatives of the following type



may be used as the olefinic constituent in the diene synthesis. These olefins are prepared easily by condensation of aldehydes or ketones with malonic ester. Compounds of this type react readily with butadiene, 2,3-dimethylbutadiene, cyclopentadiene and 1,3-cyclohexadiene.



In Table II are some of the substituted malonic esters and the yields of the addition products formed with the indicated dienes.

Table II

R'	R"	Diene	Per cent Yield
-H	$-CH_3$	1,3-butadiene	56
-H	$-CH_3$	2,3-dimethylbutadiene	80
-H	$-CH_3$	1,3-cyclopentadiene	70
-H	$-C_6H_5$	2,3-dimethylbutadiene	--
-H	$-CH(CH_3)_2$	2,3-dimethylbutadiene	--
-H	$-CH_2CH_3$	2,3-dimethylbutadiene	--
-H	$-CH_3$	1,3-cyclohexadiene	--

Alkylidene- and arylidene-cyanoacetic esters, -malononitriles, -acetoacetic esters, and the ethyl ester of ethylenetetracarboxylic acid all add normally to 1,3-dienes. Representatives of these reactions are given in Table III.

Table III

Olefin	Diene	Per cent Yield
$CH_3CH{=}C(CN)(CO_2C_2H_5)$	$CH_2{=}C(CH_3)C(CH_3){=}CH_2$	67
$C_6H_5CH{=}C(CN)_2$	$CH_2{=}C(CH_3)C(CH_3){=}CH_2$	86
$CH_3CH{=}C(COCH_3)(CO_2C_2H_5)$	$CH_2{=}CHCH{=}CH_2$	86
$CH_3CH{=}C(COCH_3)(CO_2C_2H_5)$	$CH_2{=}C(CH_3)C(CH_3){=}CH_2$	82
$C_2H_5OCH{=}C(COCH_3)(CO_2C_2H_5)$	$CH_2{=}C(CH_3)C(CH_3){=}CH_2$	62
$(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$	$CH_2{=}C(CH_3)C(CH_3){=}CH_2$	90
$(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$	$CH_2{=}CHCH{=}CH_2$	72

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PHYSICAL PROPERTIES AND CHEMICAL CONSTITUTION METHYLCYCLOHEXANE AND THE MULTIPLANAR STRUCTURE OF THE METHYLCYCLOHEXANE RING

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Various unsuccessful attempts to prove the existence of stereo isomers of cyclohexane and its derivatives have been carried out. Qudrat-i-Khuda's claim that 4-methylcyclohexane-1-acetic-2-carboxylic acid could be obtained in four forms was not confirmed by Goldschmidt and Gräfinger, and Dey and Linstead have shown that his second form of β,β-dimethylcyclohexanone is in reality 2,4,4-trimethylcyclopentanone, a molecular rearrangement having taken place in the Clemmensen reduction of the dimethyldihydroresorcinol. It seems very likely that one of the alleged acetylcyclohexanes obtained by Zelinsky and Tarassowa contains or is a methylacetylcyclopentane. Furthermore, Adams and Miller were unable to isolate more than one form of 4,4-dimethylcyclohexane-1,1-diacetic or -1-carboxylic-1-acetic acid or 4-methylcyclohexane-1,1-diacetic acid in spite of an exhaustive search. It would, therefore, appear that the author's results supply the first direct experimental evidence for the existence of the simple cyclohexane ring in multiplanar forms.

The authors have obtained physical data on a large number of organic compounds. Their most recent work was done on cyclic compounds, namely, cyclopentane, cyclohexane, cycloheptane and some derivatives. Three forms of methylcyclohexane were described. They were called the A, B, and B' forms. The A form was produced from either 1-methyl-Δ^1-cyclohexene or 3- or 4-methylcyclohexanol. The B form was prepared from 2-methylcyclohexanol by reduction. Upon standing several days or upon warming to 40-60° the B form changed to a B' modification, having slightly different physical properties. The densities and refractive indices of these three forms are shown in Table I.

Table I

	A	B	B'	B'
d_4^{20}	0.7704	0.7679	0.7694	0.76944
n_C^{20}	1.42167	1.42081	1.42093	1.42085
n_D^{20}	1.42410	1.42306	1.42316	1.42310
n_F^{20}	1.42915	1.42839	1.42846	1.42838
$n_{G'}^{20}$	1.43301	1.43230	1.43250	1.43285

The fourth column in this table shows values obtained for methylcyclohexane produced by hydrogenation of pure toluene at 150° under 100 atmospheres pressure in the presence of nickel-kieselguhr as catalyst. These values were obtained independently by Wibaut, Langedijk, Smittenberg and Hoog. This work seems to further indicate that the B' form is a stable modification of methylcyclohexane.

By further experimental work the authors have shown that the methylcyclohexanes A were slightly impure forms of B', for their physical properties changed appreciably during six months standing, and redistillation over sodium afforded material with properties closely agreeing with those originally recorded for B'. Furthermore the physical properties of form B' remained unchanged after keeping for one year.

Clemmensen reduction of pure 2-, 3-, and 4-methylcyclohexanones gave products with widely varying physical properties but was found to be due to the presence of small quantities of methylcyclohexenes, since on further reduction with hydrogen and Adams' platinum catalyst, the physical properties agreed closely with those originally recorded for B'. These results seem to indicate beyond all doubt the existence of the B' form, but no evidence could be obtained in these experiments for the B modification.

Reduction of the pure semicarbazones of 2- and 4-methylcyclohexanones with sodium ethoxide by a modification of the Wolff-Kishner method led in both cases to the B modification, which passed on standing for several days into the B' form.

3-Methylcyclohexanonesemicarbazone yielded upon reduction apparently anomalous results for which no satisfactory explanation can be offered. This does not, however, exclude the possibility of the presence of varying quantities of another isomeride of methylcyclohexane. These experiments seem to establish the existence of at least two forms of the methylcyclohexane ring, one stable and one unstable.

The exact number of theoretically possible forms of methylcyclohexane has been discussed by Brodetsky and by Cohen Henriquez. According to the former, the "chair" or "Z" form of the cyclohexane ring can give rise to two isomeric monosubstituted derivatives, while the latter finds that there is one fixed ("Z") modification and an infinite number of mobile modifcations of which the "C" form is one. Both mathematical analyses appear to be in agreement that more than two forms of the mono-substituted six-membered ring are theoretically capable of existence.

The following table shows the densities and refractive indices of the hydrocarbons obtained by reduction of the semicarbazones of corresponding ketones. Measurements were made immediately after preparation and also some days later. Yields from the semicarbazones varied from % to %.

Table II

	4-Methylcyclohexanone		2-Methylcyclohexanone	
	Immed.	5 Days	Immed.	3-4 Days
d_4^{20}	0.7676	0.7695	0.7678	0.7694
n_C^{20}	1.42090	1.42104	1.42083	1.42099
n_D^{20}	1.42311	1.42326	1.42306	1.42321
n_F^{20}	1.42847	1.42856	1.42835	1.42853
$n_{G'}^{20}$	1.43238	1.43256	1.43224	1.43253

	Experiment 1		Experiment 2	
	3-Methylcyclohexanone		3-Methylcyclohexanone	
	Immed.	5 Days	Immed.	Several Months
d_4^{20}	0.7699	0.7718	0.7716	Remained
n_C^{20}	1.42102	--	1.42096	unchanged
n_D^{20}	1.42326	1.42321	1.42321	
n_F^{20}	1.42854	--	1.42855	
$n_{G'}^{20}$	1.43248	--	1.43240	

Experiment 3

	3-Methylcyclohexanone		
	Immed.	7- Days	
d_4^{20}	0.7687	0.7701	Remained un-
n_C^{20}	1.42098	1.42099	changed on further
n_D^{20}	1.42321	1.42321	standing or after
n_F^{20}	1.42848	1.42852	redistilling over
$n_{G'}^{20}$	1.43239	1.43247	sodium.

The results of the experiments carried out on the ketones by use of Clemmensen reduction are shown in Table III. The yields of hydrocarbon in these reductions were about 60%.

Table III

	2-Methyl-cyclohexanone	3-Methyl-cyclohexanone	4-Methyl-cyclohexanone
d_4^{20}	0.7735	0.7770	0.7704
n_C^{20}	1.42291	1.42504	1.42196
n_D^{20}	1.42516	1.42737	1.42426
n_F^{20}	1.43061	1.43296	1.42962
$n_{G'}^{20}$	1.43466	1.43725	1.43365

These same ketones were reduced with hydrogen and Adams' platinum catalyst. Results are shown in Table IV.

Table IV

	2-Methyl-cyclohexanone	3-Methyl-cyclohexanone	4-Methyl-cyclohexanone
d_4^{20}	0.7694	0.7693	0.7692
n_C^{20}	1.42091	1.42093	1.42092
n_D^{20}	1.42316	1.42316	1.42316
n_F^{20}	1.42844	1.42847	1.42848
$n_{G'}^{20}$	1.43242	1.43243	1.43238

Some methylcyclohexane was also prepared by reduction of 1-methyl-Δ'-cyclohexene with hydrogen and Adams' platinum catalyst. Its properties are shown in Table V.

Table V

	1-Methyl-Δ'-cyclohexene
d_4^{20}	0.7698
n_C^{20}	1.42121
n_D^{20}	1.42346
n_F^{20}	1.42880
$n_{G'}^{20}$	1.43237

The authors hope to obtain further evidence for the existence of the various forms of methylcyclohexane by the determination of freezing points.

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CONDENSATIONS BROUGHT ABOUT BY BASES

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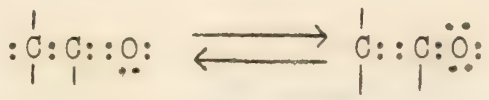
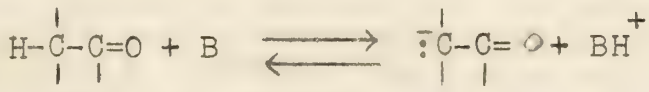
A series of eight articles which have been published by Hauser since 1937 discusses various aspects of the acetoacetic ester, Claisen, and Perkin condensations. These reactions all are quite similar and are considered to proceed through the intermediate formation of enolates. Thus, in the presence of a base a proton is removed from the group H-C-C=O to form a negative enolate ion which may exist in either of the two resonance forms (a and b):

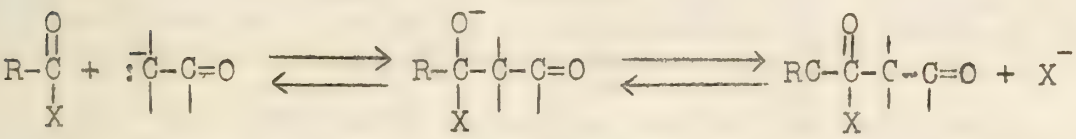


(a) (b)

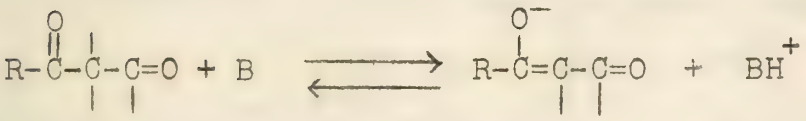
The carbon to carbon condensations which take place in the Claisen and Perkin reactions may be represented most simply as the reaction of a with the carbonyl group of a molecule which has not been converted into an enolate.

The Claisen condensation may be represented by the general equilibrium equations, where B is a base:





I II



In the light of these equations, Hauser suggests as a general definition that any carbon to carbon condensation between a metallic enolate and a compound of the type RCOX may be classified as a Claisen condensation.

Component I may be an ester, anhydride, acid chloride, or N-diphenylacetamide and component II may consist of the enolate ion of an ester, aldehyde, ketone, N-diphenylacetamide, or 1,3-diketo compound. The types of base B that may be used to effect the Claisen condensation include the salts C_2H_5ONa, NH_2Na, $(C_6H_5)_3CNa$, and certain Grignard reagents. It has been shown that these are true reversible equilibrium reactions; and so some driving force is necessary to make them go to completion. Several factors may contribute to this driving force:

1. Relative solubilities of the starting material and condensation product.

2. Formation of cyclic condensation products.

3. Enolization of the condensation products.

4. A decrease in basicity of the reaction mixture.

The condensation of ethyl acetate is an excellent example of one which goes to completion because of an enolization of the condensation product:

$$CH_3\overset{O}{\overset{\|}{C}}-CH_2\overset{O}{\overset{\|}{C}}-OC_2H_5 + C_2H_5O^- + Na^+ \rightleftharpoons CH_3\overset{O^-}{\overset{|}{C}}=CHCOOC_2H_5 + C_2H_5OH + Na^+$$

III

The acetoacetic ester (III) is a stronger acid than the ethyl alcohol formed by the enolization so that the equilibrium will lie on the side of the sodium enolate and this enol formation may be thought of as the driving force of this reaction.

Some condensations have been reported, however, in which enol formation of the product is impossible. In such cases, it has been observed that a much weaker base is present at the end of the reaction than was used to instigate the condensation. Observation of many Claisen condensations reveals that this decrease in basicity of the reaction mixture is of fundamental importance to the ability of the reaction to go to completion.

The base that will effect a particular condensation is limited by this factor of decreasing basicity of the reaction mixture, solubilities of the compounds formed, etc. Furthermore, the base B may enter into a side reaction with the carbonyl compound to give an intermediate ion which may decompose thus:

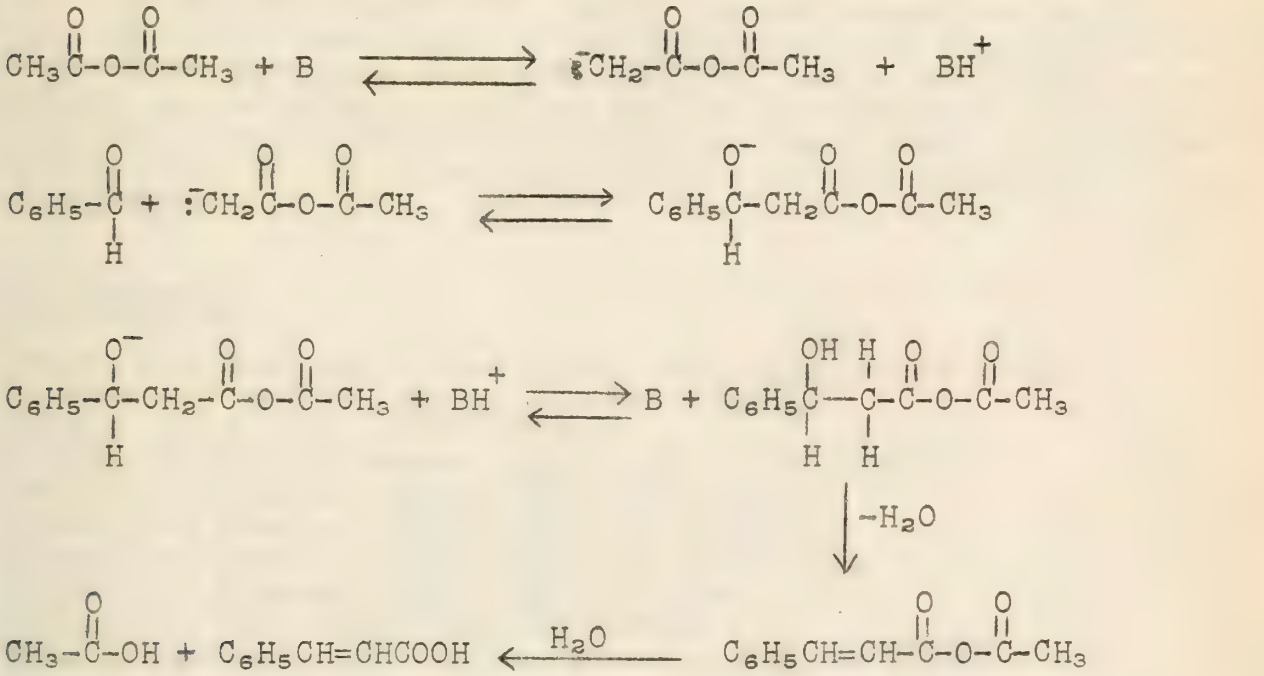
$$R-\overset{O}{\overset{\|}{\underset{X}{\underset{|}{C}}}} + B^- \rightleftharpoons \left[R-\overset{O^-}{\overset{|}{\underset{X}{\underset{|}{C}}}}-B\right] \longrightarrow RCOB + X^-$$

This reaction becomes very important when X corresponds to a weaker base than B. Thus, the very low yield of acetoacetic ester obtained from ethyl acetate in the presence of sodamide probably is due to the predominance of such a competing reaction between the NH_2^- and the carbonyl group of the ester:

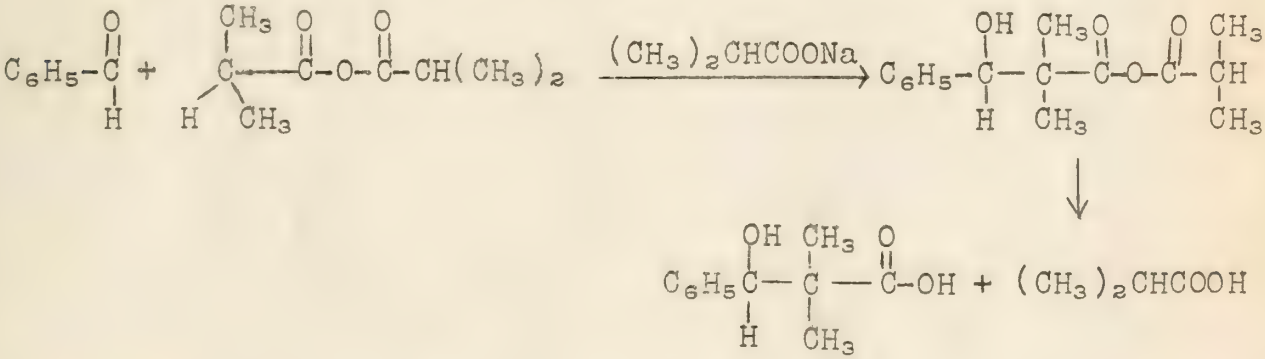
$$CH_3\overset{O}{\overset{\|}{C}}-OC_2H_5 + NH_2^- \rightleftharpoons \left[CH_3\overset{O^-}{\overset{|}{\underset{OC_2H_5}{\underset{|}{C}}}}-NH_2\right] \longrightarrow CH_3\overset{O}{\overset{\|}{C}}-NH_2 + C_2H_5O^-$$

In certain cases, this competing reaction of base B with the carbonyl compound may be minimized by first converting the system H-C-C=O into its enolate ion and then adding the compound we wish to react with this enolate. This is the technic used by Hauser in his condensations.

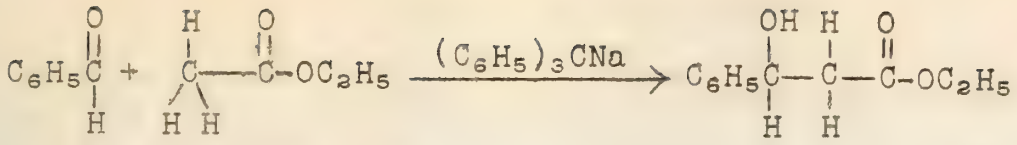
The Perkin condensation is very similar to the Claisen condensation in that it is brought about by bases, proceeds through the primary formation of an enolate, and consists of a series of equilibrium reactions which may be represented generally thus:



Here it is the loss of water which drives the reaction to completion. Evidence for the formation of the intermediate "aldol" was furnished by Fittig in 1885 when he reported the isolation of an "aldol" incapable of losing water:



Müller and his coworkers recently reported that they were unable to duplicate this experiment of Fittig. However, Hauser has repeated Fittig's experiment and succeeded in isolating the aldol. He then went further and was successful in isolating an aldol from the condensation of ethyl acetate and benzaldehyde:



Apparently this is the first case of the Perkin type of condensation in which a cinnamic acid derivative is formed that has been arrested at the aldol stage.

It may be noticed that in the general equations written above for the Perkin reaction, the anhydride has been represented as the form which condensed with the aldehyde, while the sodium salts merely act as a basic catalyst for the condensation. This point has long been a controversial one, and Hauser has done much to show definitely that the anhydride and not the sodium salt does condense.

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RELATIONSHIPS BETWEEN ULTRAVIOLET ABSORPTION SPECTRA AND STRUCTURE IN ORGANIC COMPOUNDS

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The use of ultraviolet absorption spectra in the identification and analysis of organic compounds has achieved increasing emphasis in recent years. The purpose of this report is to review some of the generalizations which may be made concerning the structure of simple organic compounds from a study of ultraviolet absorption spectra, and to point out some of the practical applications in which this method may be valuable.

Absorption spectra usually are indicated graphically by plotting wave lengths or frequencies as abscissas against the extinction coefficients, or their logarithms, as ordinates. In ultraviolet absorption studies of organic compounds, measurements usually are made on solutions of the compounds, and broad absorption bands without much detail are obtained. Compounds thus studied are commonly characterized by the wave lengths and the intensities at which maximum absorption occurs. The extinction coefficient is a measure of the intensity of absorption and is calculated by the formula:

$$\varepsilon = \frac{1}{c \cdot d} \log \frac{I_0}{I}$$

where ε is the molecular extinction coefficient, c is the concentration in moles per liter, d is the thickness of the cell in centimeters, I_0 is the intensity of the incident light and I the intensity of the light transmitted. The solvent always should be indicated also, since it sometimes exerts a profound effect on the values obtained.

The simplest chromophoric group which shows selective absorption in the measurable ultraviolet region is the ethylenic double bond which, in the case of ethylene, has the values indicated in the table (1). Modification of this compound by replacement of the hydrogen atoms by alkyl groups shifts the maximum a few mμ toward the longer wave lengths. This is the general effect of substitution where only the weight of the molecule is increased and no additional chromophoric groups are introduced. If the double bond becomes part of a ring, the shift toward the visible region is more pronounced, as shown in the case of bornylene (2). The spectra of the ethylenic alcohols and amines are very similar to those of the simple ethylenes.

If an additional double bond is introduced into the compound, it has little effect on the position of maximum absorption, if the double bonds are not in conjugation. The intensity of absorption, however, is practically doubled (3). This also is a general effect, that is, if two or more isolated chromophoric groups are present in a molecule, the individual spectra are unchanged except in intensity, and that only if the chromophoric groups are alike. The increase in the value of ε is approximately additive, so this affords a possible means of determining the number of isolated double bonds in a molecule.

Table

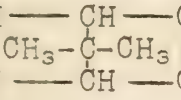
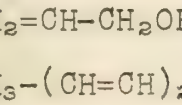
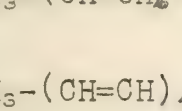
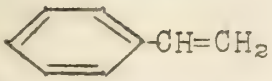
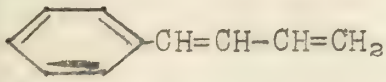
	Compound	Solvent	Absorption in Shorter Wave Lengths		Absorption in Longer Wave Lengths	
			Max.	ε	Max.	ε
1.	$CH_2=CH_2$	--			about 180	about 10,000
2.		--			198-204	--
3.	$CH_2=CH-CH_2-CH_2-CH=CH_2$	alcohol			under 185	about 20,000
4.	$CH_2=CH-CH_2OH$	hexane			189	7,600
5.	$CH_3-(CH=CH)_2-CH_2OH$	alcohol			under 232	--
6.	$CH_3-(CH=CH)_3-CH_2OH$	alcohol			268	53,100
7.	$CH_3-(CH=CH)_4-CH_2OH$	alcohol			310	44,700
8.	$CH_2=CH-CH=CH_2$	hexane			217	21,000
9.		hexane			225	20,000
10.	$CH_3-CH=CH-CH=CH-CH_3$	alcohol			under 232	--
11.		ether			260	4,500
12.		heptane			255	220
13.		hexane			245	15,200
14.		hexane			280	24,400
15.	CH_3COCH_3	hexane chloroform alcohol methanol water	187	920	279 277 272 270 264.5	14.8 17 15.2 15.5 17.4
16.	$CH_2=CH-CH_2-CH_2COCH_3$	--			278	28

Table - Continued

	Compound	Solvent	Absorption in Shorter Wave Lengths		Absorption in Longer Wave Lengths	
			Max.	ε	Max.	ε
17.	$CH_3-CH=CHCOCH_3$	alcohol	220	10,400		
18.	$(CH_3)_2C=CHCOCH_3$	hexane	229.5	12,600	327	39.9
		ether	230	12,600	326	39.9
		alcohol	237	12,600	318	87
		methanol	238	10,700	315	55
		water	244.5	10,000	312	96
19.	$CH_3-CH=CH-CHO$	hexane	205	16,100	329	18.4
		alcohol	218	15,600	320	19.5
20.	$CH_3-CH=CH-COOH$	hexane	208	12,200		
		alcohol	204	11,500		
21.	$CH_3-(CH=CH)_2-COOH$	hexane	261	25,200		
		alcohol	254	24,800		
22.	$HOOC-CH=CH-COOH$	alcohol	210	13,000		
23.	CH_3COOH	hexane			198	63
		alcohol			204	44.5

If conjugated double bonds are present in a compound, the position of maximum absorption shifts 30-50 mμ toward the visible region for each additional conjugated double bond, although the amount of the shift diminishes somewhat as the number of double bonds increases. The value of ε usually increases somewhat, but not markedly. This also is a general effect of increasing conjugation in a molecule, and is illustrated by compounds 4, 5, 6, and 7.

The effect of substitution in conjugated dienes is, in general, the same as in simple ethylenic compounds, that is, a shift of the maximum toward the visible region occurs, the amount of the shift depending on the size and character of the substituent. Substitution of the hydrogen atoms on the ends of the conjugated system seems to produce a greater effect, and the incorporation of the diene system into a ring produces a marked shift toward the longer wave lengths, being approximately equal in effect to adding another conjugated double bond in a straight chain. Ring closure also lowers the value of ε considerably (compounds 8, 9, 10, and 11).

Aromatic compounds are unique in their absorption spectra as well as in their chemical properties, and cannot be regarded as unsaturated cycloaliphatic compounds, as a comparison of absorption

data for benzene (12) and octatrienol (6) clearly shows. The absorption spectra for benzene is split into eight well-defined bands, only the most intense one of which is indicated in the table, while octatrienol gives only one broad, structureless absorption band. The benzene nucleus is considered to be a distinct chromophoric system, and similarly, for other aromatic nuclei such as naphthalene, phenanthrene, etc., separate series of compounds must be set up if data is to be compared.

Substitution of saturated groups in the benzene nucleus has the usual effect of shifting the maximum somewhat toward the visible region. In addition, the fine structure of the benzene spectrum is more or less destroyed depending on the character of the substituent. The following substituents are listed in the order of increasing ability to destroy this fine structure: $-Cl$, $-OH$, $-OCH_3$, $-OC_2H_5$, $-NH_2$. Polysubstitution of benzene produces additional bathochromic effects with increasing numbers of substituents. In the case of the disubstituted benzenes, no generalizations are possible except that the largest bathochromic effect is achieved in the p-compounds.

If the benzene nucleus is substituted with an unsaturated group which is not in conjugation with the ring, the usual rules of substitution apply. If, however, the unsaturated group is in conjugation with the ring, in the simplest case (13) a slight shift of the maximum toward shorter wave lengths occurs, together with a large increase in the value of ε, and the loss of fine structure in the spectrum. If additional double bonds are introduced, the effect is the same as increasing conjugation in an ordinary ethylenic compound, and the benzene ring is equivalent in its effect to about 1.5 double bonds (14).

A saturated aliphatic ketone shows two bands of absorption in the region 180-300mμ (15). Since the band occurring in the shorter wave lengths is difficult to measure, it will be disregarded. The effect of substitution on the spectra of ketones is the same as for ethylenic compounds. Solvents, however, exert a unique and consistent effect in the case of ketones. Solvents with increasing polar character always shift the longer wave length absorption band of ketones toward the shorter wave lengths (15).

Unsaturated ketones are similar to saturated ketones in their spectral behavior if no conjugation is present (16). If α,β-unsaturation exists, however, the absorption band shifts strongly toward the red end of the spectrum, and a new absorption band appears at 220-250mμ which has much larger ε values (17). The presence of this absorption band of unusually high intensity in the spectra of ketones in the region 220-250mμ is an almost infallible indication of α,β-unsaturation. The use of solvents with increasing polar character exerts a bathochromic effect on the maximum in the shorter wave lengths, while the lower frequency maximum is shifted toward the shorter wave lengths (18). This behavior toward solvents is useful also in identifying these compounds. A further means of identification is the fact that their semicarbazones give spectra in which the maxima are always shifted 20-30mμ farther toward the visible region.

Aldehydes are very similar to ketones in their spectral behavior. They also show two absorption bands in the same region as those of the ketones (19). The use of alcohol as a solvent for aldehydes produces far-reaching changes in the spectra due to acetal formation.

Carboxylic acids first show selective absorption at 200-210 mμ. Ley believes that the two absorption bands of ketones are shifted far toward the extreme ultraviolet when the carbonyl group is transformed to a carboxyl group. In that event a second maximum of higher intensity should occur in the extreme ultraviolet. However, measurements cannot be made in this region since the solvents themselves show absorption at these wave lengths.

The effect of substitution is the same for acids as for the other chromophoric groups discussed. Solvents with increasing polar character shift the maxima toward the red end of the spectrum in the case of acids (23). The esters, on the other hand, behave like ketones in this respect, and their maxima are shifted toward the shorter wave lengths. In all other respects, the spectra of esters resemble those of the acids very closely.

The conjugated unsaturated acids are similar to α,β-unsaturated ketones in that their absorption is shifted into the longer wave lengths, and a second maximum of higher intensity appears in the shorter wave lengths. However, in their behavior toward solvents they differ from the conjugated ketones. The higher frequency maximum shifts still higher, while the longer wave length maximum shifts toward the red end of the spectrum when solvents of greater polar character are used (20). The unsaturated dicarboxylic acids are very similar to the monocarboxylic acids. The second carboxyl group produces a much smaller shift toward the longer wave lengths than does an addition conjugated double bond (21 and 22).

Ultraviolet spectroscopy has been an almost indispensable aid in the identification and analysis of certain natural products. In the field of the natural polyenes, Kuhn and Karrer have shown the usefulness of this method. It is especially useful for calculating the number of double bonds in a molecule, and Kuhn has worked out a set of rules to be used in this connection. The discovery of the conversion of ergosterol and 7-dehydrocholesterol into D vitamins by irradiation with ultraviolet light greatly stimulated the use of ultraviolet absorption spectra as a means of investigating the structure of the sterols and steroids, and much valuable information has been obtained from these studies.

Besides its use in the establishment of structure of natural products, ultraviolet spectroscopy is useful in analytical work, that is, for the detection of impurities and the determination of the degree of purity of a compound. It has been used for distinguishing cis-, trans-isomers, the trans-form having an absorption slightly farther toward the red end of the spectrum. Since ultraviolet absorption measurements do not entail decomposition reactions, they may be used for studies of tautomerism and determination of reaction kinetics.

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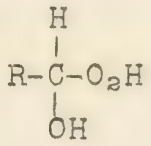
Reported by Frederick Grosser
March 6, 1940.

SOME ORGANIC-PEROXYGEN COMPOUNDS

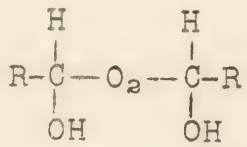
Rudolph Crigee -- Technische Hochschule, Karkruhe
Alfred Rieche -- Universtät, Leipzig

It is not safe to generalize about the chemistry of peroxides. Although many compounds of this type have been encountered, their instability has made purification difficult. In many cases there is a good chance that the properties ascribed to the peroxide are those of impurities. Many materials have been called peroxides merely because of their instability or because of qualitative color reactions. However, in certain cases, careful purification and quantitative studies of properties have yielded reliable information. This paper will deal principally with such cases.

Rieche's work on peroxides had as its most important result the establishment of the structure of ozonides. He showed that hydrogen peroxide adds to the carbonyl group of aldehydes as any HX compound does. If equimolecular quantities of reactants are used an hydroxyalkyl peroxide (I) results. A second molecule of aldehyde can be used to form a dihydroxydialkyl peroxide (II).

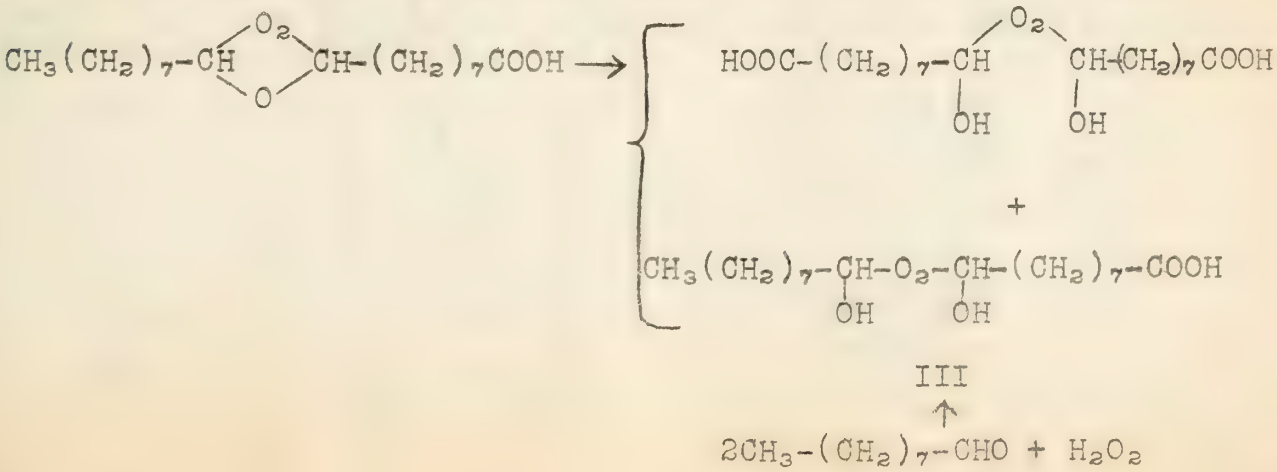


I



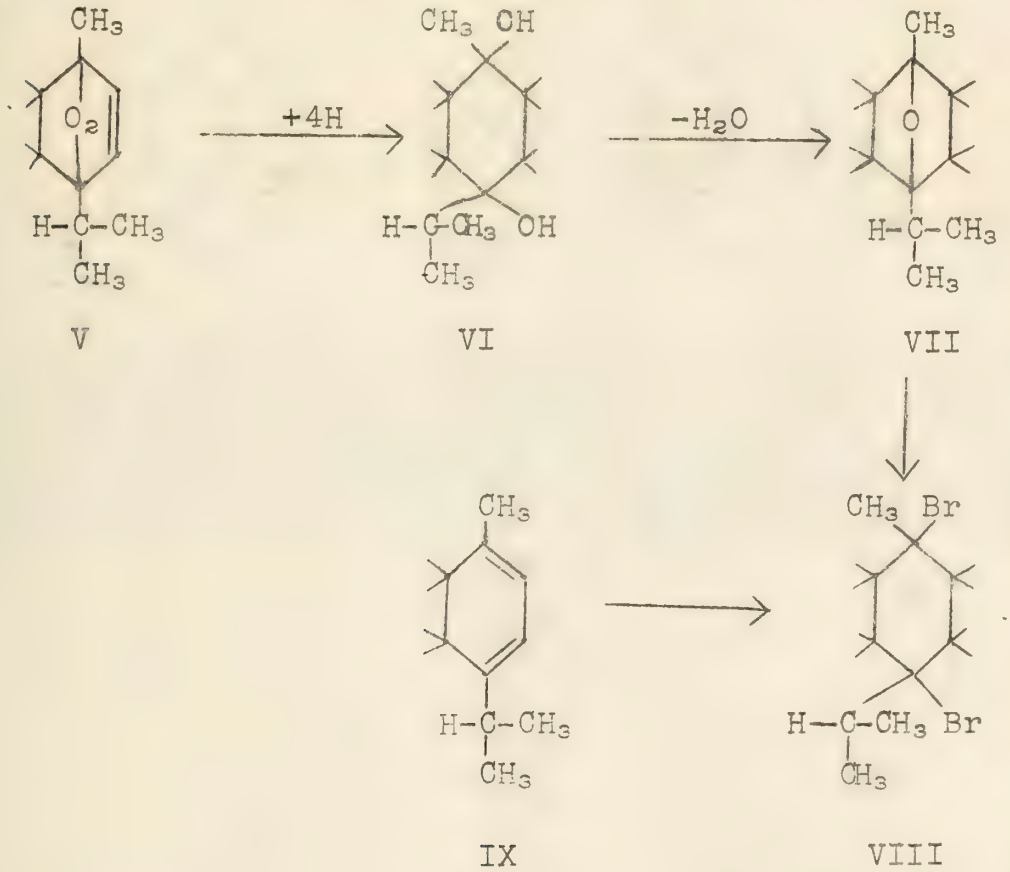
II

The lower members of these series are highly explosive liquids. The higher homologs are solids and have lost much of the explosive character. For example, di-(alphahydroxynonyl) peroxide (III) is sufficiently stable to be recrystallized from petroleum ether and to give a satisfactory melting point (74°). This molecule is one of the products of mild hydrolysis of oleic acid ozonide (IV). From the ozonide of an unsymmetrical olefin two symmetrical dihydroxylalkyl peroxides are produced rather than the one unsymmetrical peroxide. Attempts to synthesize the ozonides themselves by dehydration of the dihydroxyalkyl peroxides have given no information for the products of such attempts are, like the ozonides, unstable material having the consistency of honey.

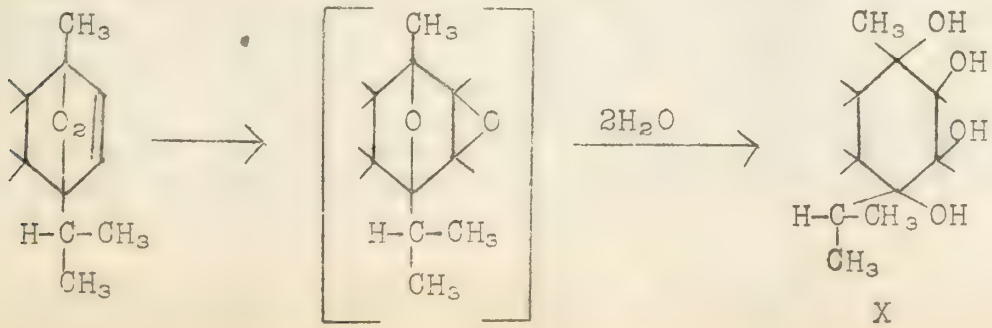


III

In studying the "aromatic" distillate of the goosefoot plant, Nelson and Wallach reached the surprising conclusion that this natural product is primarily a peroxide. The pure substance is called ascaridole. The assignment of structure V is based on the following facts. It is a liquid terpene derivative of composition $C_{10}H_{16}O_2$. Neither of its oxygen atoms can yield derivatives characteristic of alcohols, aldehydes or ketones. When heated to 150°, it undergoes violent reaction and the temperature rises rapidly to 250°. In the presence of palladium four atoms of hydrogen are absorbed. The resultant product is a dihydric alcohol (VI) which on dehydration yields 1,4-cineol (VII). The proof of the structure of ascaridole depends on the conversion of VII to the known crystalline dihydrobromide (VIII) of the menthadiene (IX).



Like many alkyl peroxides, ascaridole is unstable toward acids. At room temperature dilute sulfuric acid causes rearrangement to an erythritol (X).



Ascaridole is stable towards heat below 150°, since it is purified by distillation at 96-97° and 8 mm. Kharasch has used ascaridole in his study of the effect of peroxides on the direction of addition of HX to an olefin.

The action of oxygen in the presence of mercury vapor radiation transforms certain compounds into materials which behave like peroxides. The product from tetralin is 1-perhydroxytetralin (XI). Since this molecule, like simple alkyl hydrogen peroxides, is acidic, isolation is accomplished by alkaline extraction followed by acidification. The product is purified by crystallization. The position of the perhydroxyl group is demonstrated by reduction to α-tetralol (XII).

XI XII

Cyclohexene peroxide has been shown to have an analogous structure (XII). Since this material is a liquid, check of its purity was made by running quantitative tests for functional groups. Addition of bromine to the olefinic linkage occurred in 94-95 per cent of the theoretical amount. Zerewitinoff determinations showed 90 per cent of the theoretical active hydrogen.

XII

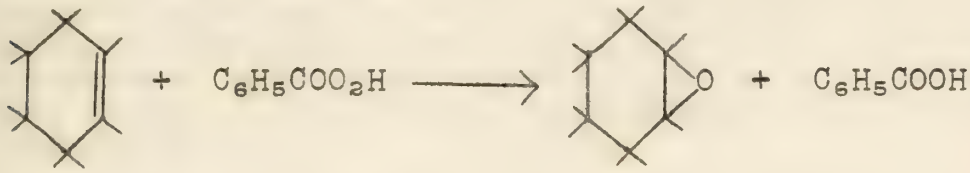
Determination of the per cent peroxidic oxygen by the reaction:

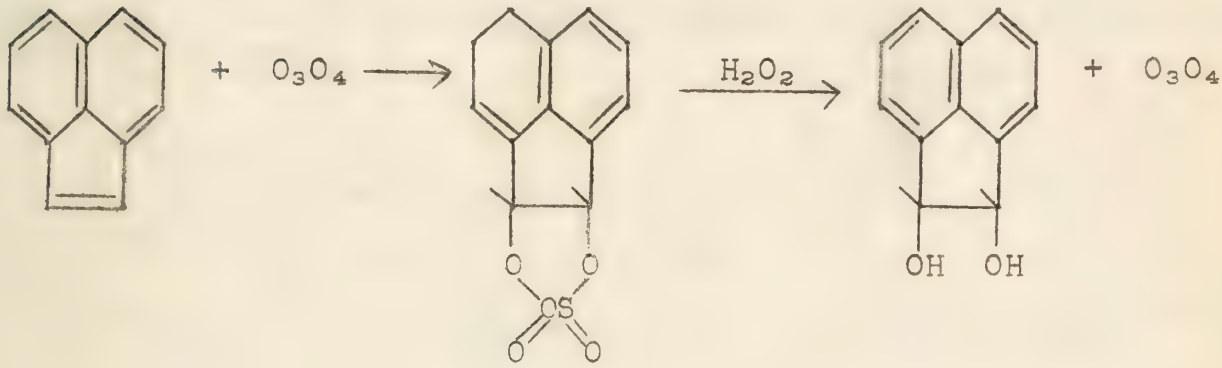
$$RO_2H + 2KI + 2HOAc \longrightarrow ROH + 2KOAc + I_2 + H_2O$$

failed because of the partial reaction of I_2 with the olefinic linkage. This reaction also is used for the estimation of the peroxides believed to be the active intermediates in the spoilage of fatty food products such as butter. There, also, the results must be in error due to the interference of the olefinic bonds of the unsaturated esters present in the fats. In addition, account should be taken of the fact that dialkyl peroxides do not give this reaction but may still cause spoilage.

Many of the other "peroxides" produced by use of active oxygen are derived from olefins, for example, from pinene, fulvene, amylene and ergosterin. The structures of the products, however, are not known.

The alpha-perhydroxy olefins just discussed decompose on standing at ordinary temperature. If the peroxide and olefin links are present in two molecules, interaction also takes place. Benzoyl peroxide is used as the catalyst in polymerization of certain olefins. The action of peracids to produce epoxides is the basis of a quantitative determination of the olefin linkage. Hydrogen peroxide, in the presence of osmium tetroxide, hydroxylates olefins to cis-glycols. In this last reaction the intermediate osmic esters can be isolated.





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Reported by J. L. Marsh
March 6, 1940.

VALENCE ANGLE STUDIES

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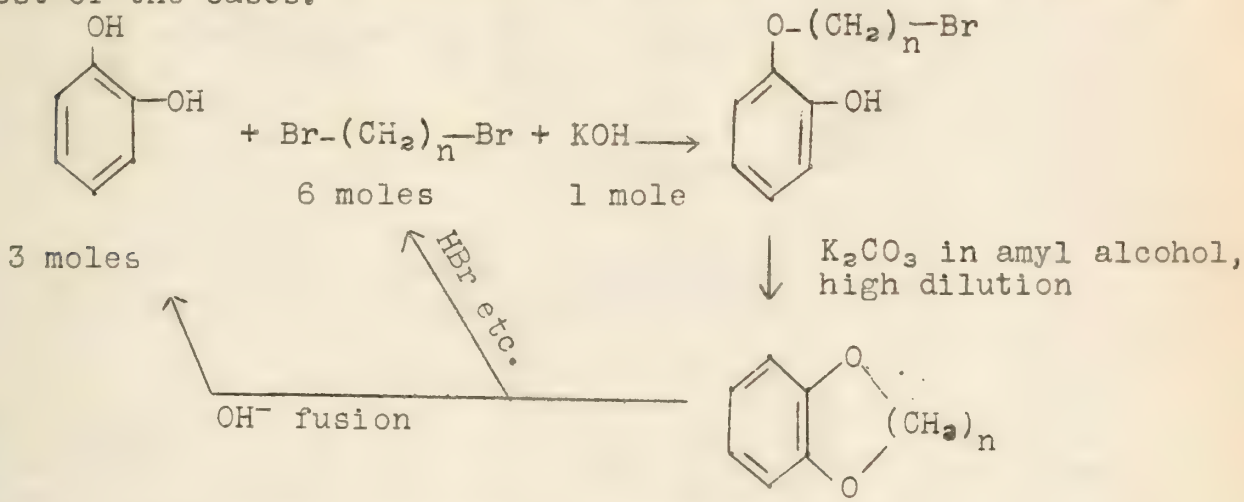
Lüttringhaus, a former coworker of Ziegler's, has used the high dilution method of ring closure to form many-membered cyclic ethers as a means of measuring chemically the distance between two hydroxyl groups in the same molecule. Thus for the first time organic chemists are enabled to adduce direct chemical evidence for structures which have been postulated previously on the basis of physical measurements and general indirect chemical phenomena. Lüttringhaus has applied this principle to the proof of rigid bond structures in a few cyclic molecules and to the determination of valence angles of CH_2 carbon, ether oxygen, sulfide sulfur, and sulfone sulfur.

I Reactions, methods, and proof of structures.

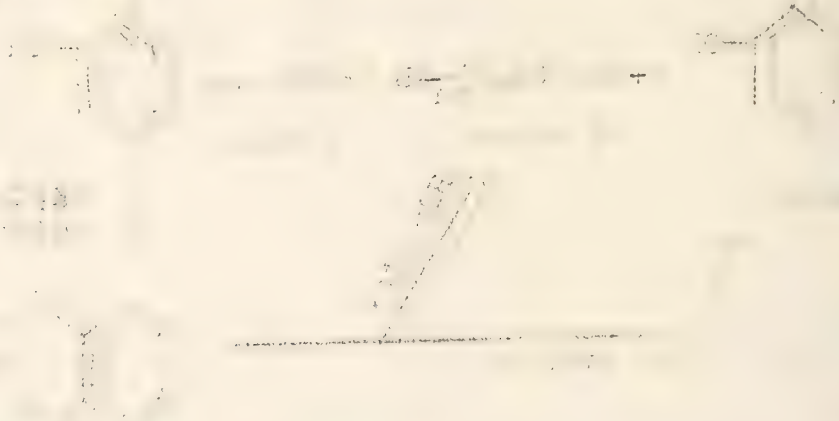
The reactions involved were used in a study of catechol which may serve to illustrate the method, identical for all the rest of the cases.



The essential features are the following:

1. Formation of the half ether under the conditions shown, with great excess of polymethylene bromide, and very little alkali. This, of course, is to prevent further reaction.
2. High dilution big ring closure.
3. Proof of structure.

   a. The product was split into the original polymethylene bromide by HBr, HI, or $AlBr_3$.
   b. The original catechol was regenerated by alkaline fusion in an inert atmosphere.
   c. Negative Zerewitinoff determination indicated that no free phenolic groups were left.
   d. Rast molecular weight determination by freezing point lowering showed that the reaction was intramolecular, and the odor indicated the presence of a ring of the correct size.

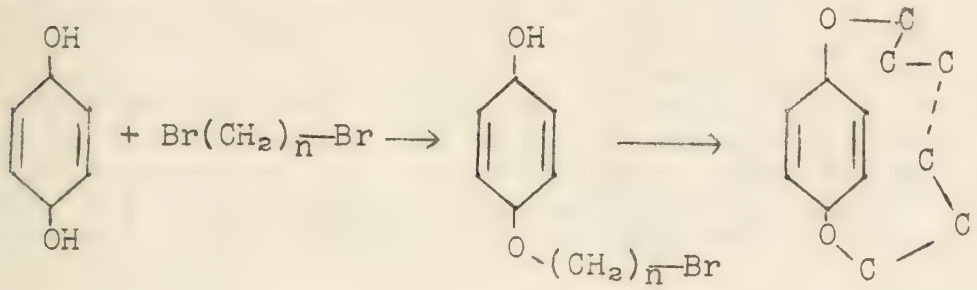


The results proved that the formation of ether rings is successful from $2 \leq n \leq 10$, with variations in yield which would be expected from the hydrogen crowding shown in the Stuart models.

II The rigidity of cyclic structures.

Various investigators have endeavored to explain experimental results by postulating altered ring structures, e.g. the Mills-Nixon effect, the Kauffler formulas for biphenyls. Lüttringhaus has, therefore, applied his new method to disprove some of these structures and has found in every case that the number of methylenes required to bridge the gap between the hydroxyls was that which stiff, unaltered paper formulas or Stuart models predicted. Conditions and proof of structures were identical with those given above. In examples which did not offer the possibility of intramolecular closure according to the models, the dimer was obtained. The results are as follows:

Hydroquinone



Starting Material	Number of Methylenes in the Aliphatic Chain					
	10	9	8	7	6	5
Hydroquinone	79		18	0*		
Resorcinol				"low"	0*	
Catechol					90	
Naphthylenes						
1,5-dihydroxy ...	61		0			
2,6-dihydroxy ...	22					
Biphenyl						
m,m'-dihydroxy ..	70					
p,p'-dihydroxy ..	0					

Yield in per cent

0* indicates that dimer was obtained

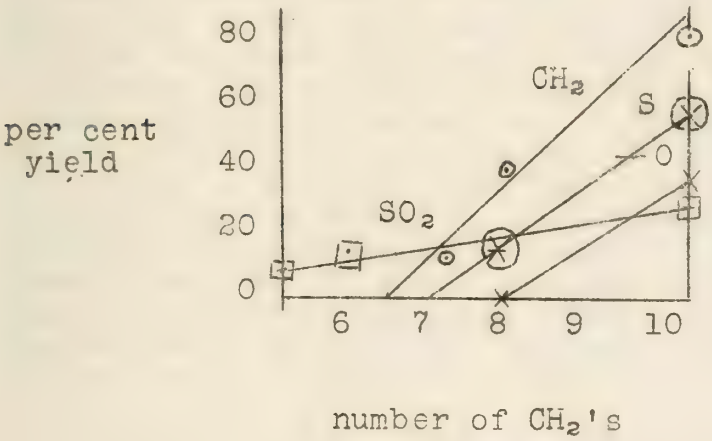
In the last case, the Stuart models predict that eleven methylenes should bridge the gap and that twelve would easily, but these have not been tried. The results in all cases indicate no appreciable alteration of the usual carbon valence, and that the oxygen angle is close to the value of 110° obtained from physical measurements.

III Application of the method to the measurement of valence angles.

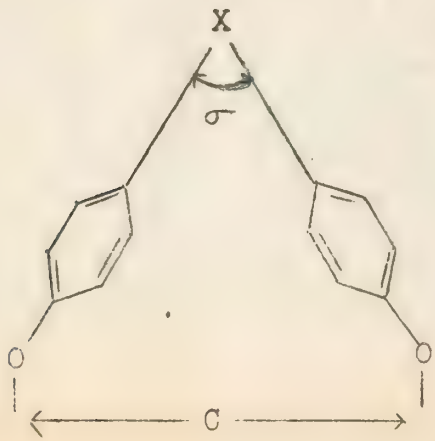
The length of the chain required to bridge a di-(p-hydroxy phenyl)-X, where X is a divalent atom, is taken as a measure of the valence angle of X.

Starting Material	Number of Methylenes in the Aliphatic Chain								
	10	9	8	7	6	5	4	3	
Di-(p-OH phenyl)-									
methane	68		27	5					Yield in per cent
ether	36		0	0					
sulfide	51		16	0*					
sulfone	24.5				10	5.7		0	

Using customary paper representation of these molecules, the angles of the central atoms were calculated. The method is ingenious. Carbon and oxygen bond lengths and angles were used as determined from electron diffraction, X-ray, rotational fine structure, Raman spectra, and several other physical measurements. It can be shown that small errors in these values have no effect on the calculated angle, and it is apparent from the figure below that the angle of X is nearly independent of the other angles. From the known data as shown, a table was arranged to show values of c in A corresponding to chosen values of X. It should be noticed that a change of ten degrees in σ corresponds to a change in c of about 0.9 which is close to the value (1.25) of the projection of a C-C aliphatic bond on a line through the atoms of the chain. Thus, the increment of one carbon does not correspond to a large change of angle and hence is a rather accurate measuring unit. The calculation then proceeds by interpolation in the table and in the yield graphs:



Values of angle σ	Theoretical distance c, assuming angle if X is- O	CH_2	S
90	6.5	6.7	6.9
100	7.4	7.6	7.9
110	8.2	8.4	8.8
120	9.0	9.2	9.6
130	9.7	9.9	10.3



Thus, the yield for 8 methylenes is 27 per cent for X as CH_2, but 16 per cent for X as S. Interpolating in the graph, we see that a theoretical 8.6 methylenes would be required for a 27 per cent yield with X as S. Now, referring to the table, we see that for the angle of 112.4° which was obtained from the X-ray data as the correct value for S in this molecule, the distance c is 9 Å. The following proportion may then be stated:

$$\frac{9\ \text{Å for X = S}}{z\ \text{Å for X = CH}_2} = \frac{8.6\ \text{CH}_2\text{'s for 27\% yield, X = S}}{8.0\ \text{CH}_2\text{'s for 27\% yield, X = CH}_2} \qquad z = \frac{9 \times 8}{8.6} = 8.4\ \text{Å}$$

This value in the table of angles and distances gives 110±3° for X as CH_2. A similar calculation for oxygen would give the value 133°, but because this involves a longer chain, a correction is necessary to allow for the fact that a methylene chain does not increase in length strictly in proportion to the number of members. The final value is then 129±4°.

This method of calculation is, however, obviously invalid for sulfone sulfur, since although the yield for a decamethylene chain is much lower, actually the ring may be closed with five members. The reason for this anomalous behavior is to be found in the comparative rates of reaction. If the dihydroxy compound in each case is allowed to react under the high dilution conditions with n-butyl bromide and the reaction rate determined by Volhard titration, the first three compounds are found nearly the same, whereas that of the last compound is about one-third of the others. This, of course, defeats the purpose of high dilution -- leading to intermolecular condensation. The angle for the sulfone is determined, therefore, by reference to the number of methylenes which will suffice to bridge the gap, and this gives the value 75°. Questioning the validity of this result, since it is somewhat smaller than the commonly accepted values, the authors suggest that it may be due to electrical effects caused by crowding of the two semipolar oxygens. They also note that such low values are bound to be doubtful because of the possibility of crowding of the aromatic rings and the methylene sidechain.

In conclusion, it might be mentioned that the angles obtained check well with the values obtained from X-ray and other studies of the atoms in question. Thus, use of measurements from these sources, particularly since, as was mentioned above, the values are not of crucial importance, seems justified. The fact that the high-dilution method is at best a complicated one with products which are difficult to obtain pure, casts some doubt on the quantitative value of the method. It should be noticed, however, that this is a measurement made chemically under actual reaction conditions, and since the results do, on the whole, check well with those obtained in other ways, the method is certainly of interest and some value.

Summary:

Benzene rings have been shown to be planar; the bonds radial and fixed within the limits of accuracy of a chemical method. The angles of S, O, and CH_2 have been measured and found to have values in close agreement with those obtained by other methods. The angle of S in SO_2 has been measured also, but is considered questionable.

S	113°	sulfide
O	129	ether
CH_2	110°	methylene
SO_2	75°	sulfone

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Reported by W. D. Fraser
March 13, 1940

THE OXYGEN OR PEROXIDE EFFECT IN THE ADDITION OF HALOGEN HALIDES TO OLEFINS

Kharasch and coworkers -- University of Chicago

Markownikoff in 1870 published two rules: (1) "if an unsymmetrical olefin combines with a hydrogen halide, the halogen adds to the carbon with fewer hydrogen atoms:, (2) by addition of hydrogen halide to vinyl chloride or chlorinated propylene, etc., the halogen will always add to the carbon which is already combined with halogen."

Exceptions to these rules were of two types: (1) clear-cut, absolute exceptions due to interaction between the carbon-carbon double bond and another unsaturated group in the molecule, as in the case of acrylic acid, and (2) indefinite exceptions in the case of hydrogen bromide subject in degree apparently to every experimental variable; allyl and vinyl halides are in this category.

In 1930 Kharasch and Mayo discovered, while working on the addition of hydrogen bromide to allyl bromide, that peroxides and oxygen catalyze the abnormal addition or addition contrary to Markownikoff's rules, explaining without exception variations of type (2) above. Such has been the amount of work done on this effect that Kharasch and coworkers have ventured to express its applicability not in terms of compounds with which abnormal addition can be obtained but in terms of those with which it cannot. They state "It now seems likely that, with certain exceptions, abnormal addition to any ethylenic bond may be observed."

Apparent exceptions are as follows: (1) Compounds containing a weakly polar double bond resulting from symmetrical substitution of groups of the same order of electronegativity. With compounds such as 2-pentene and 9-undecenoic acid reversal of addition cannot be detected because equimolar mixtures of two addition products result in the presence or absence of peroxides.

(2) Compounds in which double bonds are conjugated with carbonyl or similar groups.

(3) Compounds in which a very fast normal reaction masks any abnormal reaction. Borderline compounds in this classification may have their abnormal reactions revealed by dilution of the reaction mixture with pentane, which slows down the normal addition but presumably doesn't affect the abnormal addition proceeding by a chain mechanism, and by the use of large amounts of peroxide (as much as 10 mol per cent). 2-Butyne, styrene and trimethylethylene are examples where such a technique is successful.

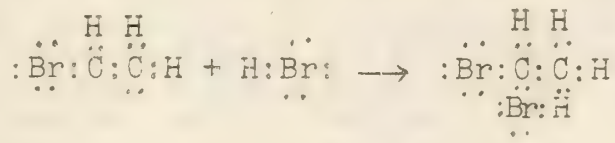
Nonterminal Double Bonds.--The above exceptions do not limit the effect to terminal double bonds, but it so happens that (1) and (3) combine to obscure abnormal addition to nonterminal double bonds much more frequently than in the case of terminal double bonds.

Decision on the Normal Reaction.--With an olefin such as trichloroethylene where no addition of hydrogen chloride or hydrogen bromide takes place under antioxidant conditions, the product resulting when the addition is catalyzed by anhydrous ferric chloride or ferric bromide is called the normal product. It has been shown that these salts accelerate the normal addition tremendously.

Solvent Effects.--Kharasch and coworkers have come to the conclusion that under strictly maintained antioxidant conditions solvents *per se* have no effect upon the direction of additions of hydrogen bromide to the ethylenic double bond, but affect markedly the rate of both modes of addition. Michael and Weiner object strenuously, but they have based their argument on the behavior of trimethylethylene which is a borderline case in exception class (3), and as such is very sensitive to changes in the relative rates of addition.

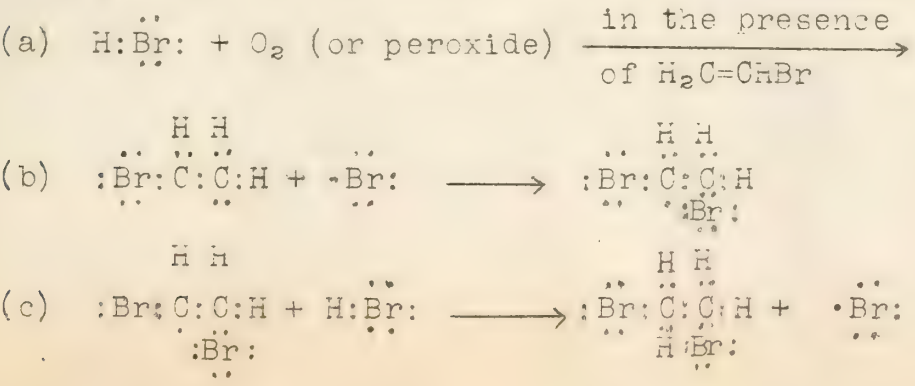
Behavior of Hydrogen Chloride and Hydrogen Iodide.--These two acids add exclusively in the normal manner, hydrogen chloride usually rather slowly unless catalyzed by ferric chloride, hydrogen iodide usually rapidly.

Mechanism.--Kharasch for his theory of the mechanism, first postulates that in a substituted ethylene the "extra" electron pair of the double bond will be displaced away from the carbon atom carrying the most electronegative radicals. The normal reaction may then be schematically represented thus in the case of vinyl bromide.



Electron diffraction data indicate a high degree of displacement at least in the case of ethylidene dichloride.

The effect of "peroxides" on the addition of hydrogen bromide to such an unsatruated molecule may be described schematically thus:



The essential features of these representations are that, in the addition of hydrogen bormide to vinyl bromide under "antioxidant" conditions, the bromide ion is directed toward the carbon atoms with the lowest electron density to yield 1,1-dibromoethane, and that under "peroxide" conditions the bromine atom is directed toward the carbon atom with the greater electron density to yield a 1,2-dibromoethyl free radical. This free radical then reacts with hydrogen bromide to yield 1,2-dibromoethane and another bromine atom, which is responsible for the propagation of the chain reaction.

Michael has raised objection to this bromine atom mechanism on the basis of the fact that peroxides do not influence the direction of addition of hydrogen iodide but do greatly accelerate it. However, Kharasch indicates that it is extremely probable that the mode of addition of hydrogen iodide under peroxide catalysis or what amounts to the same thing, by iodine, is very different from that of hydrogen bromide, that is, that iodine adds as such to give a diiodide, which reacts with hydrogen iodide to give the normal iodide and iodine.

Urushibara objects to Kharasch's mechanism for the normal addition. Some of his reasons are: (1) the completeness of the reversal of addition in many cases, (2) the catalysis of the normal reaction by platinum black, (3) the dying out of the normal reaction in a reaction mixture, containing some O_2 and which mixture shows an induction period during which the abnormal reaction supplants the normal. He postulates a chain mechanism involving hydrogen atoms for the normal additions; this is very, very improbable in solution.

In conclusion it may be said that not enough attention has been given to the possibility of activated molecules in the reaction mechanisms. As Franck and Rabinowitsch point out, the chance of having atomic mechamisms in solution is greatly reduced over that in a gaseous reaction medium.

Table of Maximum Reversal of Addition
for Various Olefins

Olefin	Peroxide	Per Cent Total Yield	Per Cent Normal	Per Cent Abnormal
Vinyl chloride	+	79	0	100
	-	81	100	0
Vinyl bromide	+	98	0	100
	-	90	100	0
Allyl bromide	+	100		95
	-	87	93	
Propylene	+	90		87
	-	95	100	
1-Butene	+	95		100
	-	90	100	
Isobutylene	+	92		89
	-	95	100	
1-Pentene	+	96		97-100
	-	84	100	0
4,4-Dimethylpentene-1	+	790	0	100
	-	790	100	0
Methylacetylene	+	100	0	100
	-	100	100	0
1-Chlorpropene	+	100	0	100
	-	91	95	
Trichloroethylene	+	91	0	100
	-	80	100	0
2-Butyne	+ (using dilution)	90		96
	-	85	100	0

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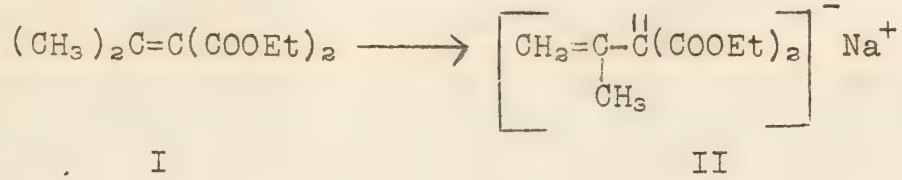
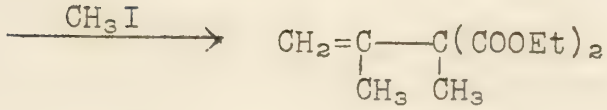
Reported by Carl M. Smith
March 13, 1940

Cope -- Bryn Mawr College

Kon and his associates, while studying three-carbon tautomerism, found that isopropylidinemalonic ester (I) reacts with alcoholic sodium ethoxide forming an enolate (II) which could be methylated to isopropenylalkylmalonic ester (III).



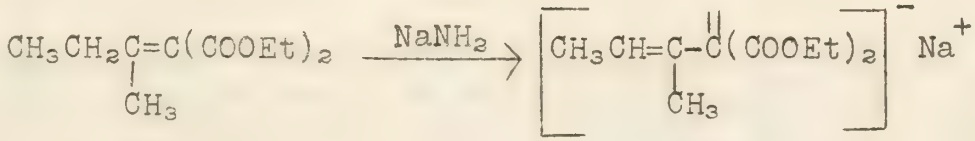
I II



III

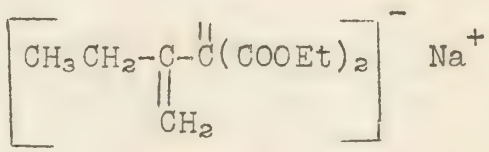
Cope, by substituting sodamide in liquid ammonia (or any inert solvent) for the sodium ethoxide in alcohol, has made this a practical synthesis for isopropenylalkylmalonic esters. The starting material (I) is obtained easily by condensing acetone with malonic ester. By substituting appropriate alkyl halides or dialkyl sulfates, compounds other than the methyl derivative (III) readily are made in yields up to 90 per cent for more active alkylating agents. The use of sodamide in ammonia decreased the alcoholysis of the product resulting under Kon's conditions.

By using 1-methylpropylidinemalonic ester (IV) (from methylethyl ketone and malonic ester), (1-methylpropenyl)-alkylmalonic esters can be similarly made. Two paths are possible for this reaction:

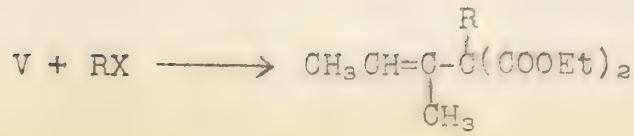


IV V

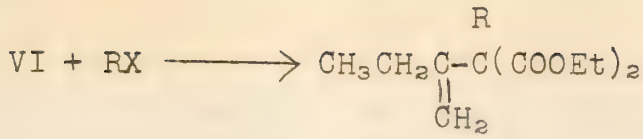
or



VI



VII

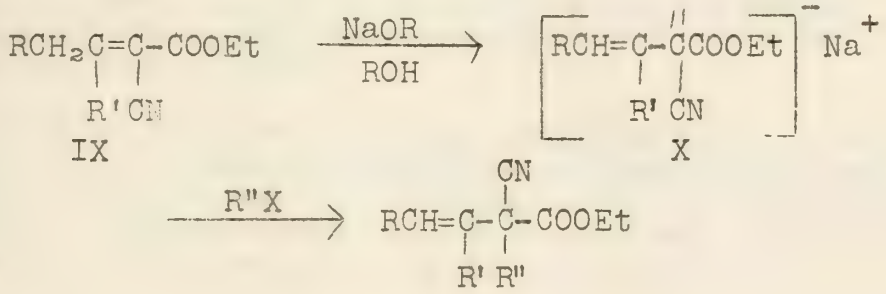


VIII

Ozonolysis of representative products (VII or VIII) showed formula VII and its precursor to represent almost exclusively the path of the reaction. Apparently both geometric isomers of VII are present.

To introduce "primary 1-alkenyl" groups, the condensation products of aldehydes and malonic ester are used. The sodamide procedure cannot be used in this series; partial decomposition results. Sodium alkoxide in alcohol is used to form the enolate which then is alkylated to the desired (primary 1-alkenyl)-alkylmalonic ester. The synthesis fails for vinyl alkylmalonic esters (due to polymerization) but, as the size of the alkenyl group increases, yields approach 90 per cent. The success of the method in this series in spite of the possibility of alcoholysis is explained as due to more favorable stearic conditions for alkylation which proceeds so rapidly as to exclude most of the side reaction.

Ketones of higher molecular weight than methylethyl ketone condense well with cyanoacetic ester but not with malonic ester so that for higher dialkylvinyl derivatives than the above (compound VII), the former ester is the basic material.



XI

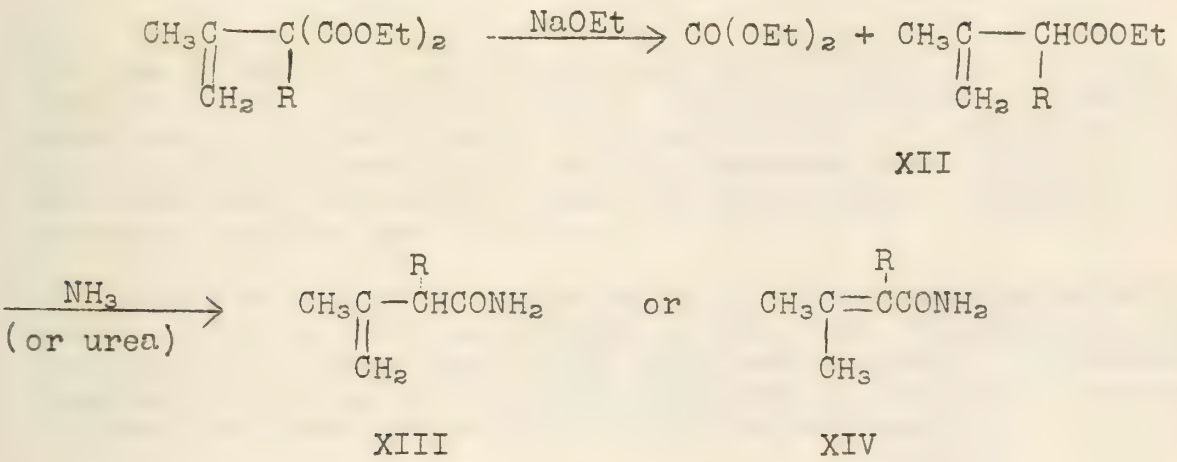
In this series also, sodamide cleaves and polymerizes the products so that sodium alkoxide in alcohol is best for forming the enolate (X). Sodium isopropoxide in isopropyl alcohol is favored since it tends to alcoholize the products less than its lower homologs. Rapid alkylation is another factor which inhibits alcoholysis. Again note that with unsymmetrical ketone-ester condensation products as starting materials, two possible enolates (X) and hence two products (XI) are possible. Ozonolysis of representative products (XI) wherein R' = methyl showed that in all cases the double bond shifted so as to be in the larger olefinic group. As expected, active alkylating agents gave best yields. Derivatives containing an R' larger than methyl (derived from diethyl and dipropyl ketones, etc.) also were prepared in better yields, probably due to more effective hindrance in these cases to alcholysis.

Condensation of these substituted vinyl esters with urea resulted in the corresponding substituted vinyl alkylbarbituric acids. Sodium ethoxide in alcohol was used as the condensing agent. Though

XI

difficulty due to alcoholysis was anticipated, good yields generally resulted from the condensations.

Isopropenylalkylmalonic esters with urea formed isopropenylalkylbarbituric acids in approximately 75 per cent yields for the lower derivatives. Small amounts of alcoholysis side products were isolated according to the following:

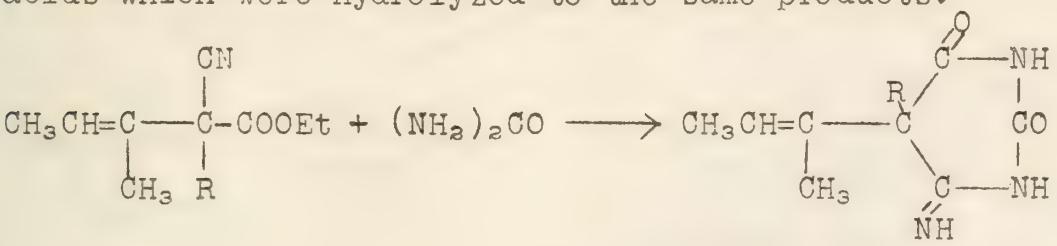


XII

XIII XIV

Monocarboxylic ester (XII) and amide (XIII or XIV) together accounted for about 15 per cent of the starting ester. The solid amide was purified easily. Ozonolysis showed it to be the α,β-unsaturated isomer (XIV).

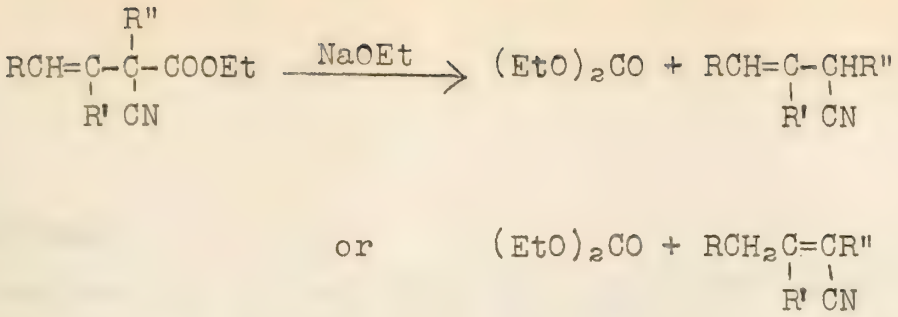
The use of (1-methylpropenyl)-alkylmalonic esters with urea similarly gave (1-methylpropenyl)-alkylbarbituric acids, this time without side products. The corresponding (1-methylpropenyl)-alkylcyanoacetic esters condensed with urea forming iminobarbituric acids which were hydrolyzed to the same products.



XV XVI

The acids from both sources was made analytically pure with ease though only after several recrystallizations were the melting points constant. This is undoubtedly due to the presence of the two geometrical isomers possible for structure XVI.

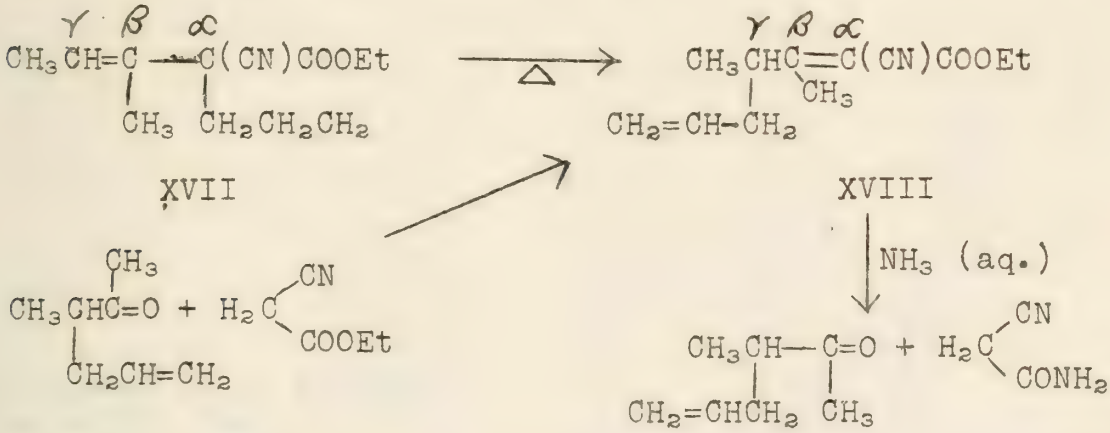
The higher (dialkylvinyl)-alkylcyanoacetic esters also combine with urea to give barbituric acids. Alcoholysis of the starting ester occurs to a considerable degree unless conditions are such as to minimize this side reaction.



The use of sodium isopropoxide and isopropyl alcohol as the condensing medium helps the yield. The substitution of guanidine for urea results in more rapid condensation though hydrolysis of the resulting di-iminobarbituric acid is somewhat more difficult than is the mono-imino derivative from the urea method. Constant melting products readily were obtained.

The structures of the substituted vinyl alkylbarbituric acids herein discussed follow from the established structures of the corresponding ester from which they were formed. Representative compounds were checked by ozonolysis and quantitative hydrogenation to known saturated barbituric acid derivatives.

The (dialkylvinyl)-alkylcyanoacetic esters prepared were all stable except (1-methylpropenyl)-alkylcyanoacetic ester (XVII) which on heating formed (1,2-dimethyl-4-pentylidine)-cyanoacetic ester (XVIII), the structure of which was established by aqueous ammonia cleavage and synthesis as shown below:



The authors explain this migration of an allyl group as analogous to the Claisen phenylallyl ether rearrangement wherein an allyl group on an electron-attracting element (O) undergoes an α,γ-shift to a carbon atom with simultaneous shifting of the double bond to the α- or electron-attracting atoms. In this case, the α- or electron-attracting atom is carbon, rendered so by virtue of attachment to CN and COOEt groups. The double bond shifts so as to become conjugated with these groups. As in the Claisen rearrangement, a cyclic intramolecular change is postulated which results in inversion of the allyl group.

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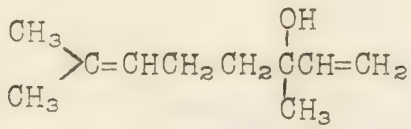
Reported by J. W. Meier
March 20, 1940.

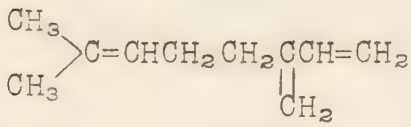
The word terpene may have a very broad significance, often being used to designate any hydrocarbon of the formula $(C_5H_8)_x$, and often other compounds of a similar nature. I propose to confine this paper almost entirely to the <u>terpenes proper</u>: hydrocarbons of the formula $C_{10}H_{16}$. These may be divided into four classes--acyclic, monocyclic, bicyclic, and tricyclic.

The acyclic terpenes are for the most part rather unstable, having a marked tendency to cyclize. Although several occur naturally, only one of them, myrcene (II), has been synthesized. Ruzicka has synthesized linalool (I) through the reaction of sodium acetylide on methyl heptenone.



I

Passing this over copper at 140° converts it to myrcene (II).

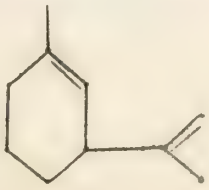


II

The chemistry of the monocyclic terpenes is complicated by the ease with which almost every one of them isomerizes. Furthermore, it is believed that almost none of the natural terpenes is composed of only one isomer.

Perkin has synthesized dipentene (<u>dl</u>-limonene, III), carvestrene (<u>dl</u>-sylvestrene, IV), <u>iso</u>-carvestrene (V), $\Delta^{3,8}$-<u>p</u>-menthadiene (VI), $\Delta^{1,8}$-<u>o</u>-menthadiene (VII), $\Delta^{2,8}$-<u>m</u>-menthadiene (VIII), and $\Delta^{3,8}$-<u>m</u>-menthadiene (IX).

III



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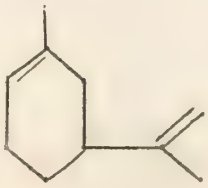

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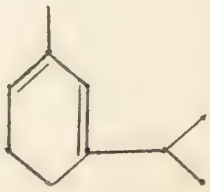
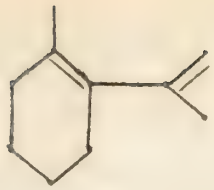
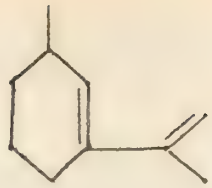


V

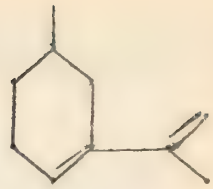
VI



VII

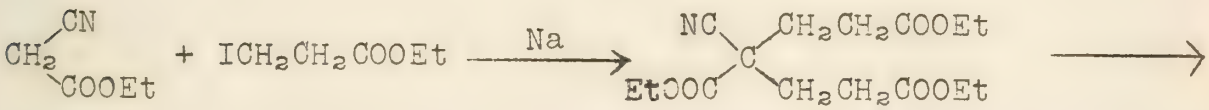


VIII

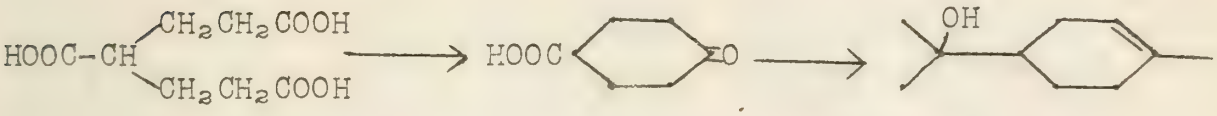


IX

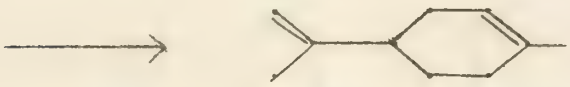
The synthesis of dipentene will serve to show his general method, which was similar for all. Cyanoacetic ester was condensed with ethyl-β-iodopropionate, giving X. This, on hydrolysis, lost a carboxyl, giving XI; heating with acetic anhydride, cyclized to XII. This, on treatment with a large excess of methyl magnesium iodide, gave terpineol (XIII), which is easily dehydrated to dipentene (III).



X

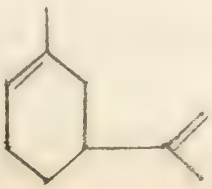


XI XII XIII



III

Dimerization of isoprene may give dipentene or diprene (XIV) according to the conditions. The compound XV has been reported also, but this is unconfirmed.

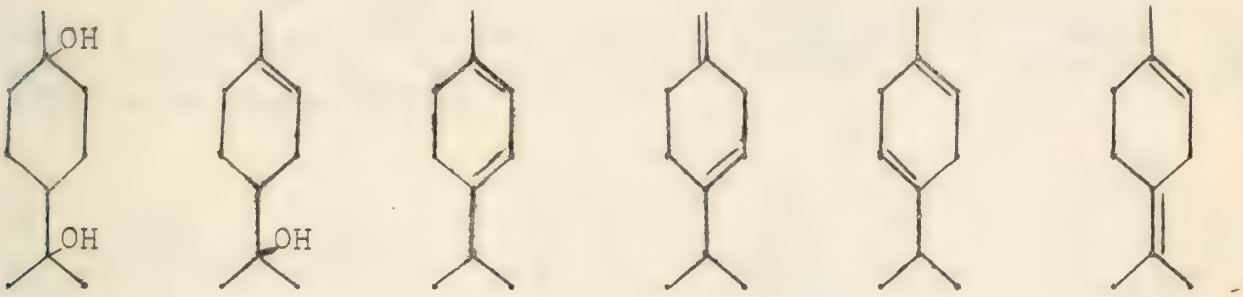


XIV

XV

The formula given for diprene is doubtful. It is the same as one of the possible formulas for iso-carvestrene, although the two are not the same compound. Carvestrene also is thought by some to be a mixture of the compounds of formulas IV and XIV.

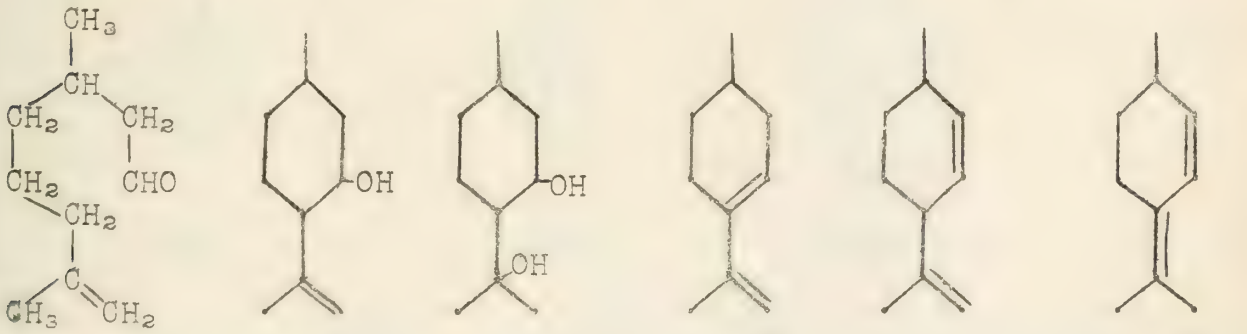
Most of the other natural terpenes can be obtained by isomerizations of limonene. Dehydration of terpin hydrate (XVI) and terpineol (XIII) (both of which readily are obtained from limonene) under various conditions may give mixtures of any of the following: dipentene (III), α-, β-, and γ-terpinene (XVII, XVIII, and XIX) and terpinolene (XX).



XVI XIII XVII XVIII XIX XX

Favorsky and Lebedeva have isolated linalool (I) and terpin hydrate from the treatment of dimethyl vinylcarbinol with sulfuric acid. As noted above, these are converted easily to terpenes.

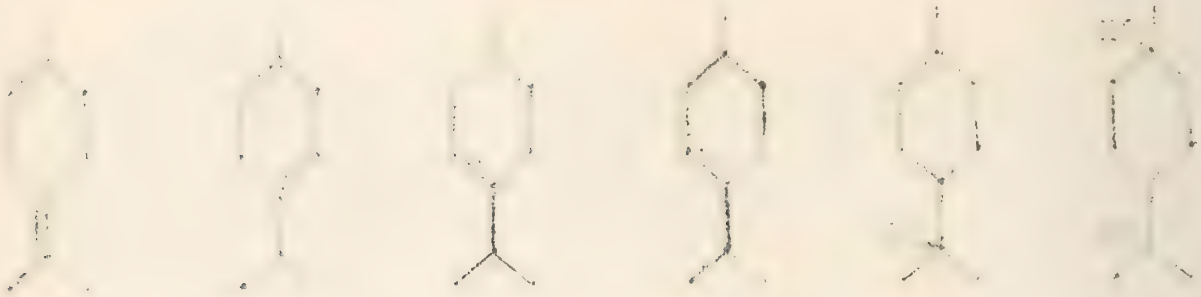
Recently Horinchi and coworkers have prepared a new terpene by cyclization of citronellal (XXI). Hydrogenation gave p-menthane. The preparative reaction must proceed through iso-pulegol (XXII), and may proceed through mentheglycol (XXIII). The three possible terpenes resulting from the dehyration of these two alcohols are represented by XXIV, XXV, and XXVI.

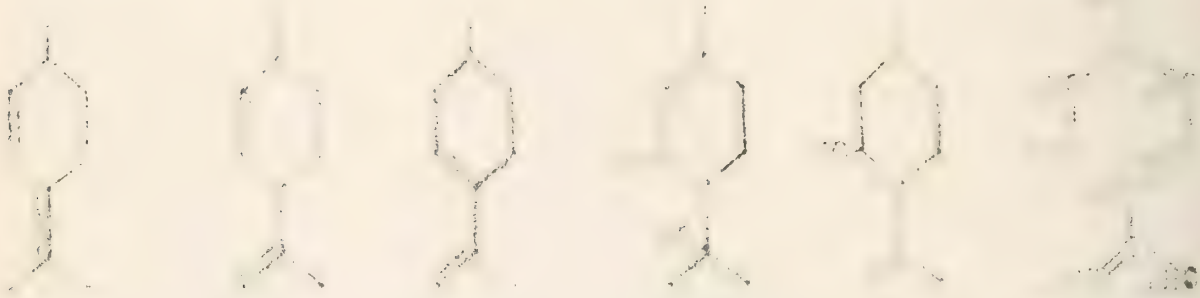


XXI XXII XXIII XXIV XXV XXVI

The terpene of formula XXIV was synthesized by Perkin, and XXV occurs naturally.

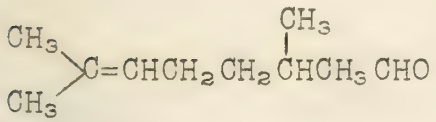
Horinchi's terpene shows an exaltation of refractive index, adds only one mol of bromine easily, and undergoes a Diels-Alder reaction readily with maleic anhydride to give an anhydride with one double bond. The conjugation of the double bonds was thus





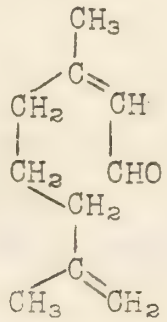
established. Color reaction led to belief in a tertiary-tertiary double bond. This was confirmed by distilling the terpene from sodium, when acetone splits off. This is a common reaction of terpenes of this type. Thus, the terpene named menogene has the structure XXVI, and its formation must, according to Horinchi, proceed through menthoglycol. However, he has accepted the formula XXI for citronellal. If the alternative formula XXVII, favored by many, is accepted, the monohydroxy compound is the only intermediate which need be postulated. Most probably citronellal is a mixture of both compounds.

By an almost identical process Horinchi has prepared and proved a new pseudoterpene, menogerene (XXVIII), of formula $C_{10}H_{14}$ from citral (XXIX). He postulated the formation of menthoglycerol (XXX)as an intermediate.

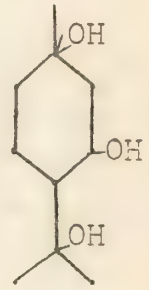


XXVII

XXVIII



XXIX

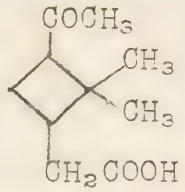


XXX

In the bicyclic series of terpenes, α- and β-pinene (XXXI and XXXII) have been synthesized from pinonic acid (XXXIII). However, since pinene and very closely related compounds are the only source of pinonic acid, the synthesis is of little importance.

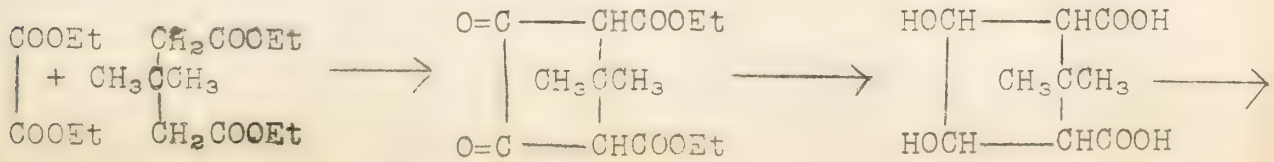
XXXI

XXXII

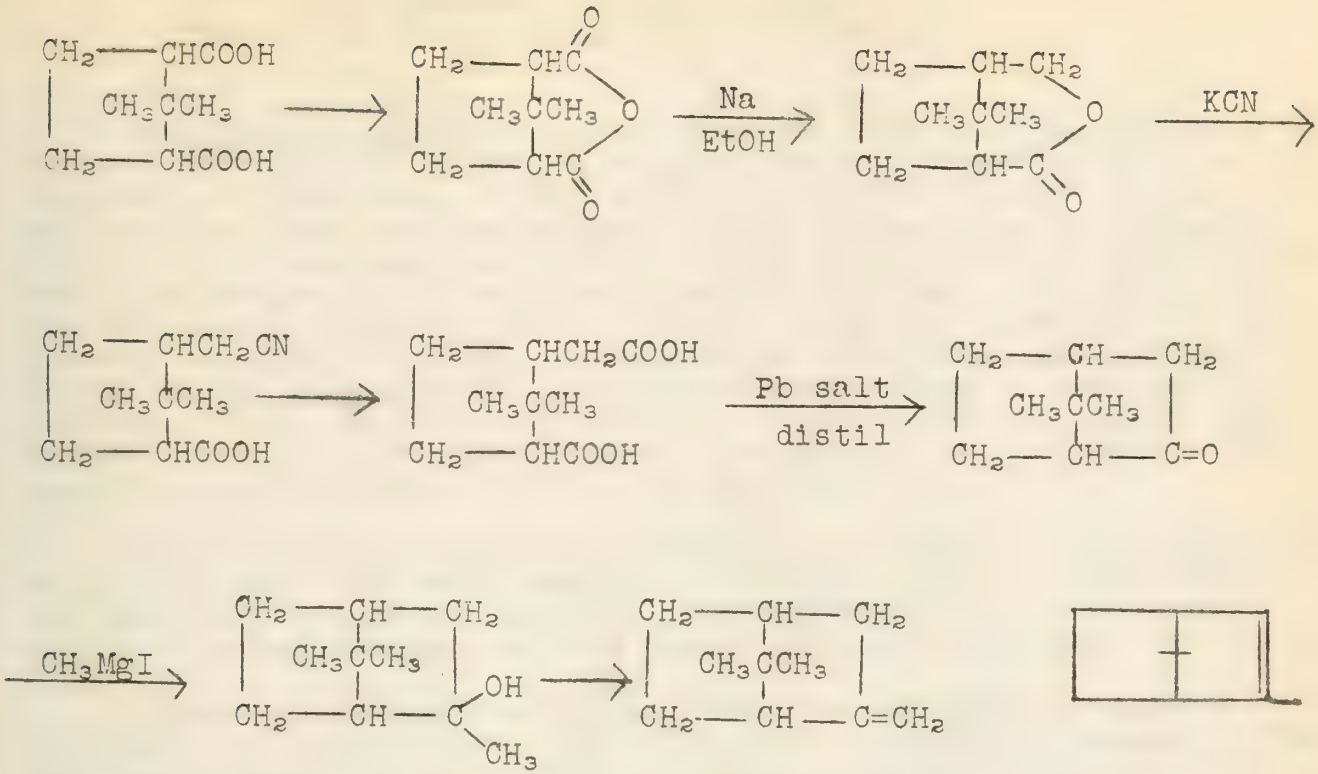


XXXIII

The only bicyclic terpene which has been totally synthesized in α-fenchene (XXXIV). Komppa synthesized this from ethyl oxalate and ethyl-β-β-dimethyl glutarate (XXV) through the following series of reactions:



XXXV



XXXIV XXXVI

None of the isomeric δ-fenchene (XXXVI) is obtained. No tricyclic terpene has been synthesized.

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March 20, 1940.

CANCER PRODUCING HYDROCARBONS

Cook, J. W., et al., Research Institute of the Cancer Hospital, London
Fieser, L. F., et al., Harvard University

Historical Aspects.--In 1775 Percival Pott called attention to the predominance of cancer in chimney sweeps, classifying it as an occupational disease. In the early part of the present century it was observed that persons engaged in the destructive distillation of coal tar were more susceptible to the development of skin cancer than similar groups of workers otherwise engaged. That the "tar cancer" arises from contact of the skin with the chemicals in the tar was confirmed in 1915 by Yamagiwa and Ichikama, who succeeded in producing cancer by the continuous application of coal tar distillates to the ear skin of rabbits. Further investigations indicated that the active substances are present in the high-boiling, neutral, nitrogen-free fraction of the distillate.

From a synthetic approach, Kennway found that tetrolin reacts with $AlCl_3$ to yield tars capable of inducing cancer. Similar tars are prepared by heating isoprene or acetylene in an atmosphere of hydrogen under pressure, and by other pyrolytic methods.

These observations indicated that the carcinogenic agents in coal tar are hydrocarbons, but all of the known hydrocarbons of coal tar tested showed no activity. A search then was instituted for a rare hydrocarbon using fluorescence spectra as a guide. A large number of hydrocarbons were thus submitted to optical examination; among them 1,2-benzanthracene (I) seemed to possess approximately the proper spectral bands. This compound, though not carcinogenic, led to the discovery of the first pure hydrocarbon of known structure, 1,2,5,6-dibenzanthracene (II), capable of inducing cancerous growth.

Determination of Carcinogenic Activity.--The technic most generally employed consists in applying the hydrocarbon in 0.3 per cent benzene solution to the skin of mice twice weekly, the application being continued till tumors are noted. A low standard concentration was adopted (0.3 per cent) to avoid difficulties associated with the low solubility of the hydrocarbons studied. To circumvent complications due to the toxicity of benzene itself, some investigators have employed the method of subcutaneous injection of a pure crystal of the hydrocarbon moistened with glycerol. More recently, solvents such as lard, sesame oil, etc., have been used for subcutaneous injections. Mice invariably are used as the test animals, largely because of the short period required for the production of their cancer. Cancer may develop after a latent period as short as sixty days in some cases, and of over a year in others. Cancerous tissue is established by histological changes and transplantation.

Structure and Activity.--The theory of the bond structure of polynuclear aromatic hydrocarbons is at present a highly controversial topic. In the correlation of structure with activity a definite point of view concerning bond structure would be advantageous. Some investigators use any of the possible Kekulé formulas

indiscriminately and noncommittally. Fieser, in the light of present evidence bases his bond structure on the Fries rule, which states that the most stable state of a polynuclear system is that in which the maximum number of rings present is in the benzenoid condition. When the Fries rule fails, as in the case of 1,2-benzanthracene, energy considerations of the quinoid structures present are used as determining factors.

With only a few exceptions the carcinogenic hydrocarbons known today contain a 1,2-benzanthracene (I) ring system. Particularly active compounds are 1,2,5,6-dibenzanthracene (II), methylcholanthrene (IV), 1,2-benzpyrene (III) and certain derivatives of these. Recently 3,4-benzphenanthrene and some of its alkylated derivatives have been discovered to possess potent carcinogenic activity.

In an attempt to correlate more firmly activity with structure and possibly to obtain information which might relate the carcinogens with other substances, a large number of substances have been synthesized which contain the active parent hydrocarbon nucleus to which is attached polar substituents. Although there is insufficient evidence at present to generalize with certainty, definite relationships are apparent. The introduction of functional groups, in general, weakens or destroys the activity of the hydrocarbon. Oxygenated groups appear to cause stronger activity than nonoxygenated functional groups in those cases in which activity is retained. Hydroxy derivatives are more potent than the corresponding methyl ethers. Acylated derivatives possess very little activity, if any. Nitro compounds are inert. One weakly active amino compound is known.

3-Hydroxymethylcholanthrene (IV) which is inactive has attracted much attention because it might conceivably arise as a product of steroid metabolism, the structure being analogous in some points to that of oestrogenic hormones, particularly equilenin. The location of the hydroxyl group seems very significant because it corresponds to the 3-hydroxyl group characteristic of the cholesterols, the bile acids and sex hormones.

Hydroaromatic derivatives of aromatic hydrocarbons of known activity are of interest in connection with the hypothesis that steroids may be converted in the animal body into cancer producing agents by transformations involving an extensive process of dehydrogenation. Since desoxycholic(V) and cholic acids from bile can be converted into methylcholanthrene by a series of chemical operations, it would be of interest to learn if any of the intermediate products are carcinogenic. Dehydronorcholene (VI), one of the almost completely saturated derivatives, was found to be inert. It may be possible that this is not an intermediate in animal degradation and this negative result casts very little light on the hypothesis of steroid conversion to carcinogens.

The most recent progress relating the steroids, particularly the sex hormones to carcinogens has been shown by the discovery of carcinogenic activity in oestrone (VII) and closely related derivatives. 4,4'-Dihydroxy-α,β-diethyl stilbene, the most potent synthetic oestrogenic substance known, has been shown to be capable of producing cancer. This is significant because this agent has the physiological action of oestrone but is not a sterol.

Synthesis.--Carcinogenic hydrocarbons can be prepared by the following methods:

1. Phthalic anhydride synthesis.

   The main steps in this synthesis consist of a condensation of a phthalic anhydride derivative with an aromatic hydrocarbon by the Friedel-Crafts method, followed by ring closure and reduction. Frequently, the keto acid must be reduced before cyclization in order to avoid rearrangements.

2. Pschorr synthesis.

   The Pschorr method, originally developed for the synthesis of phenanthrene derivatives, consists in the condensation of an ortho-nitro aldehyde with the α-carbon in a substituted acetic acid; reduction of the nitro group; diazotization; ring closure, and decarboxylation to the hydrocarbon.

3. Succinic anhydride synthesis.

   Succinic anhydride is condensed with an aromatic hydrocarbon by the Friedel-Crafts method, the keto acid reduced, the ring closed, the cyclic ketone reduced and the product dehydrogenated to the aromatic hydrocarbon.

4. Elbs synthesis.

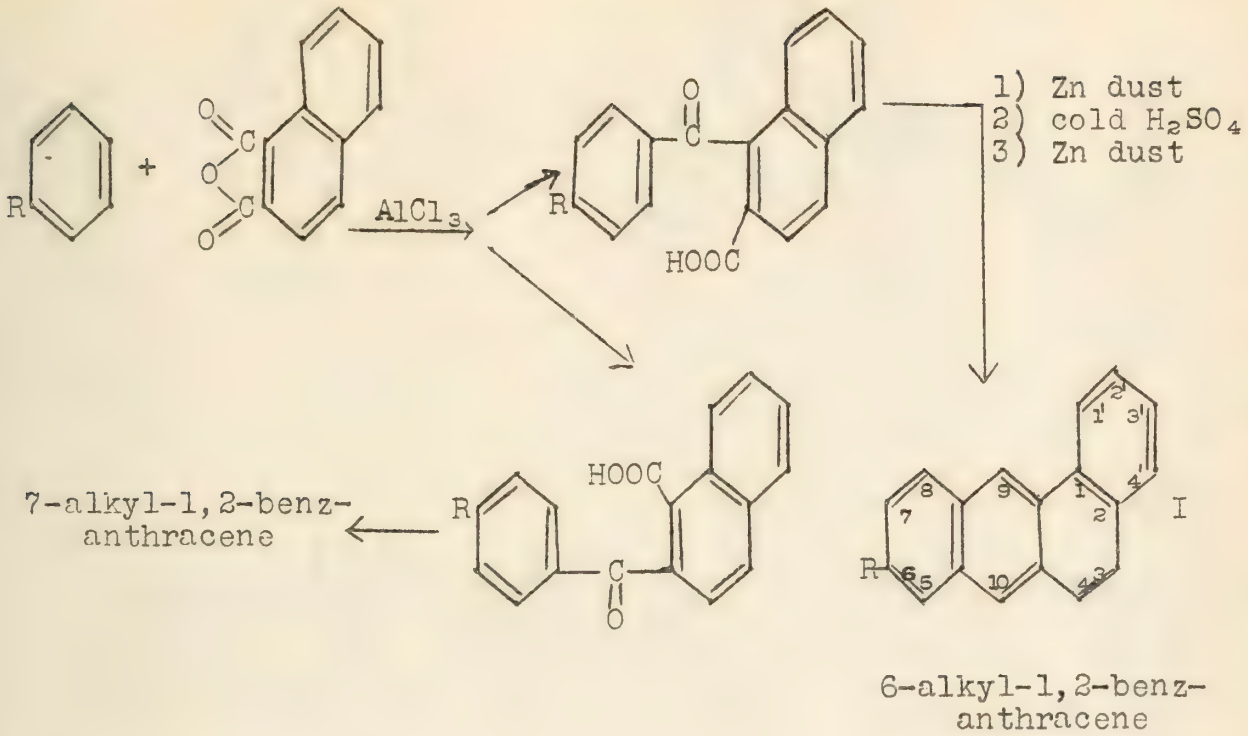
   In this method, an ortho-methyl diaryl ketone is heated whereby cyclization and loss of water occur at the same time, giving the hydrocarbon in one step. By-products and rearrangements often occur but because of the simplicity and general applicability, this synthesis has found wide use. The example given is a slight modification of this synthesis.

5. Modified Diels-Alder reaction.

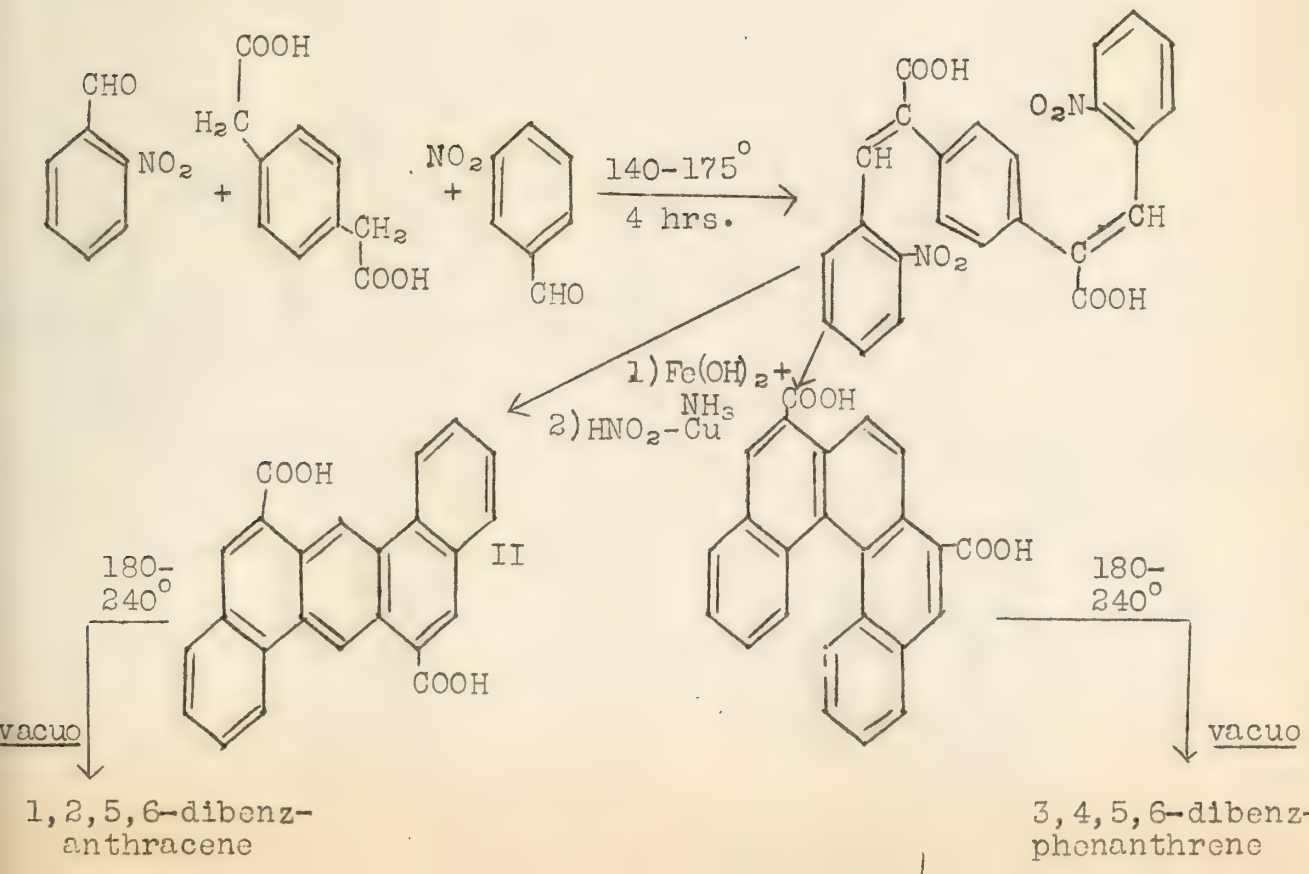
   A partially reduced phthalic anhydride derivative is condensed with a substituted butadiene by the Diels-Alder reaction, the resulting anhydride decarboxylated by fusion with alkali to a mixture of hydrogenated compounds, followed by dehydrogenation to the fused aromatic system. The yields in these reactions are generally good.

   Two other syntheses known as the Bardhan-Sengupta and the Perlman-Davidson-Bogert methods as applied to phenanthrene derivatives are less suitable and not so frequently applicable.

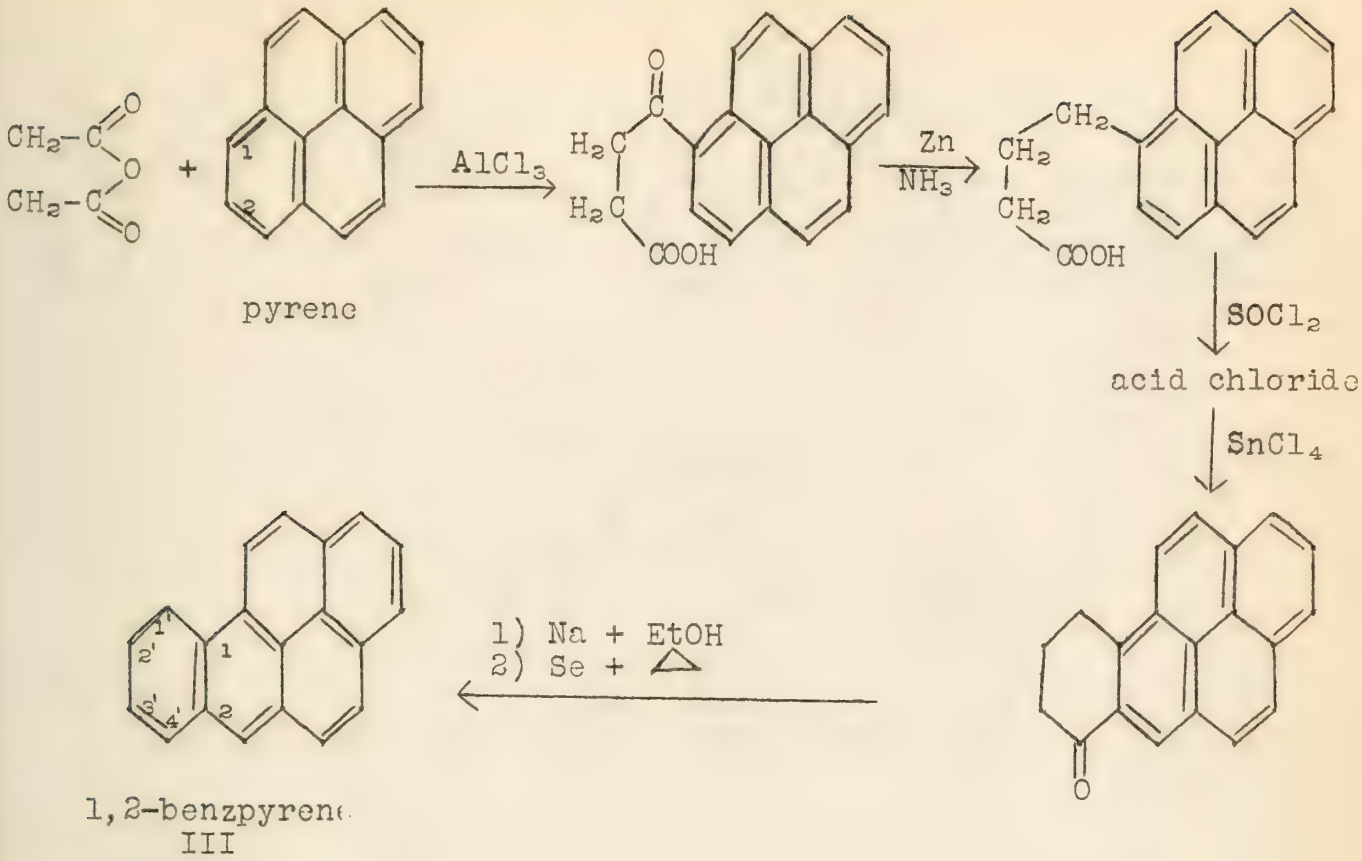
I. Phthalic anhydride synthesis.



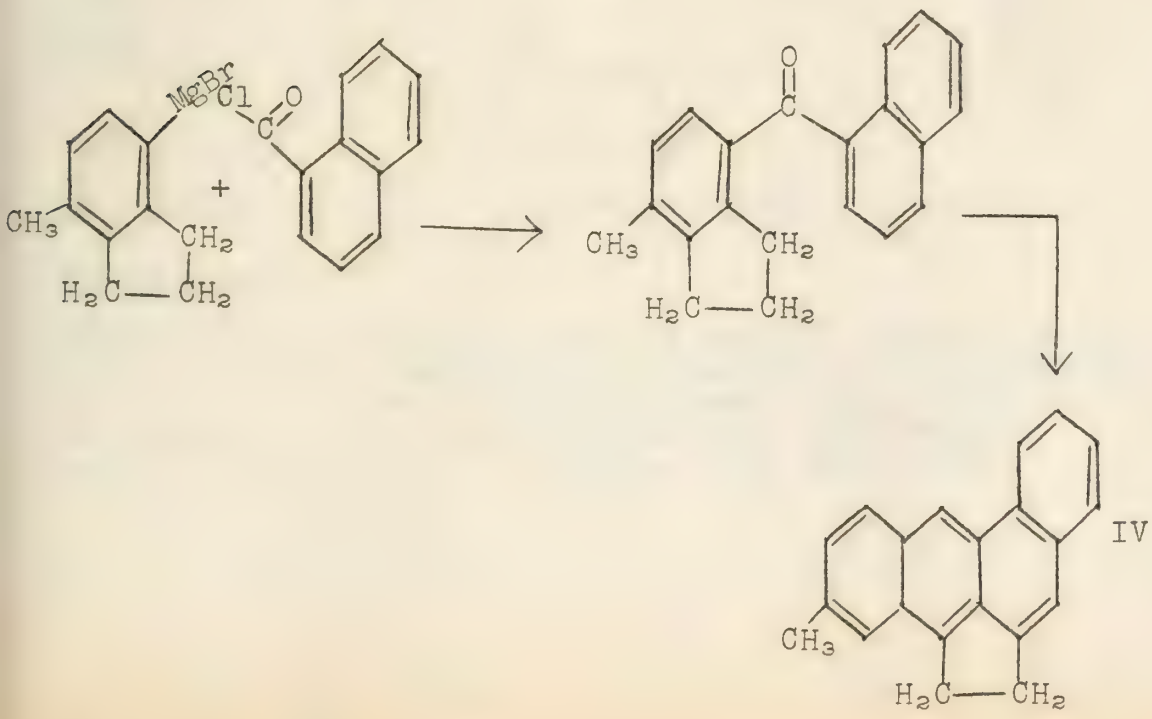
II. Pschorr synthesis.



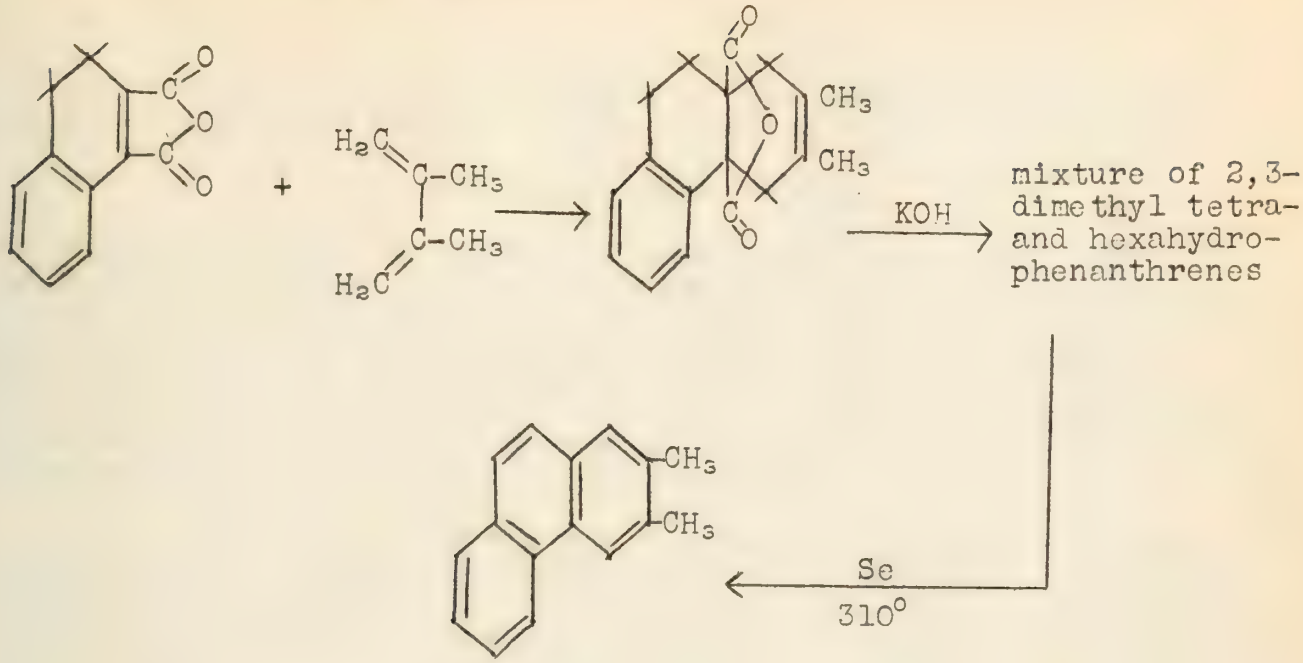
III. Succinic anhydride synthesis.



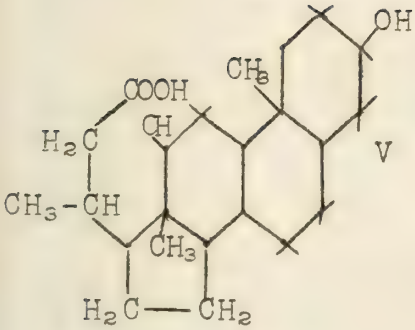
IV. Elbs synthesis.



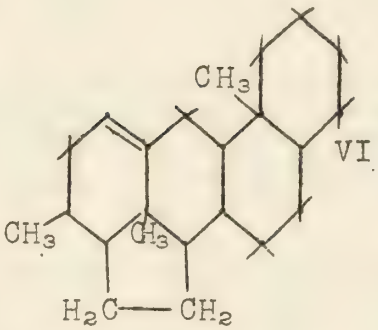
V. Modified Diels-Alder synthesis.



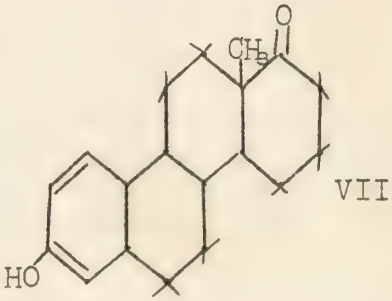
2,3-dimethyl phenanthrene



desoxycholic acid



dehydronorcholene



oestrone

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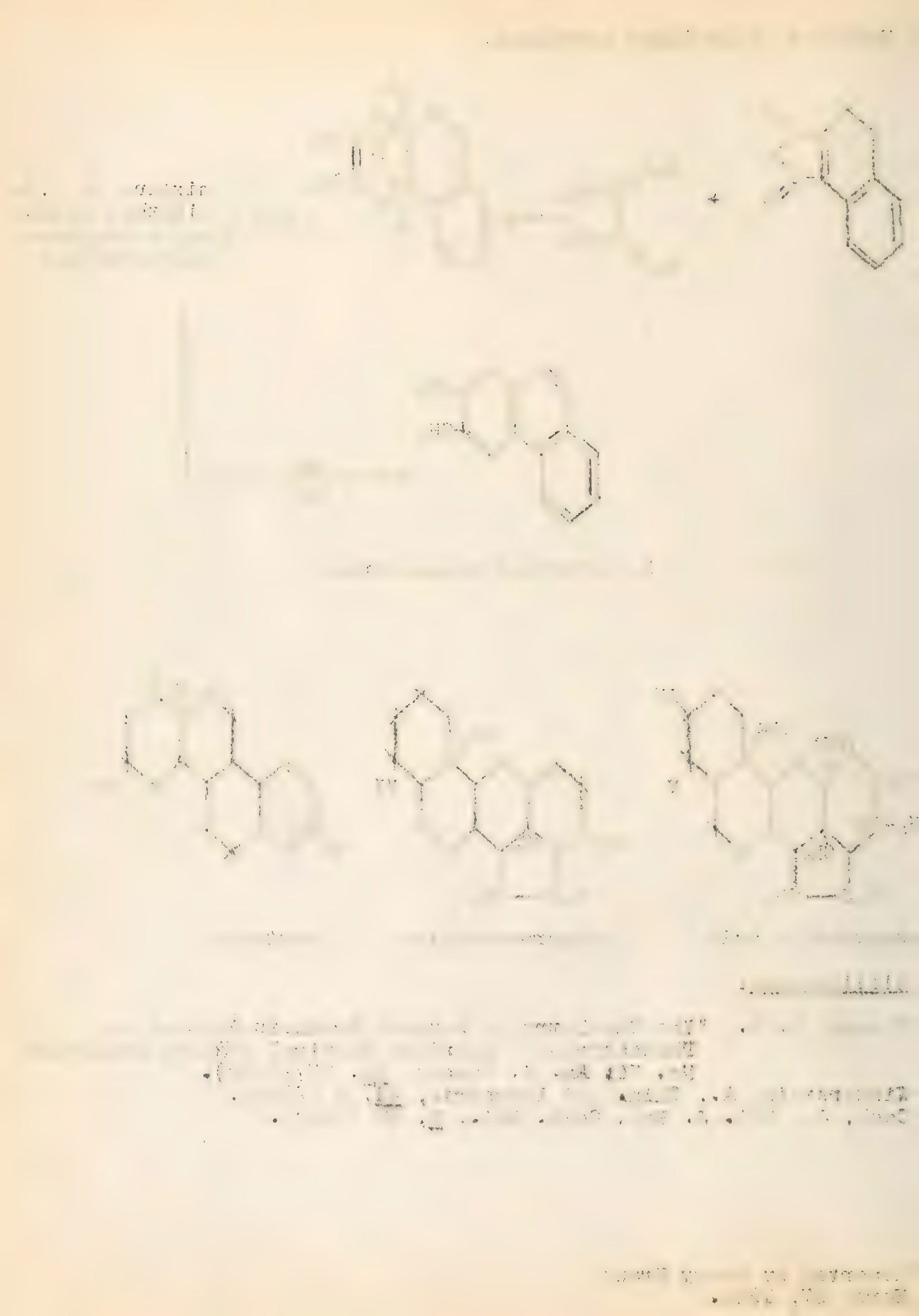
Reported by Harry Braus
March 27, 1940.



SULFURYL CHLORIDE AS A CHLORINATING AND SULFONATING AGENT

Kharasch--University of Chicago

Sulfuryl chloride is prepared by the direct interaction of sulfur dioxide and chlorine. The reaction is a reversible one and

$$SO_2 + Cl_2 \rightleftharpoons SO_2Cl_2$$

charcoal or camphor is used as a catalyst to speed the establishment of equilibrium. In the past the use of SO_2Cl_2 has depended on its dissociation to SO_2 and Cl_2 thereby serving as a source of molecular chlorine and it has been utilized almost exclusively for the chlorination of aromatic nuclei usually in the presence of halogen carriers. The use of SO_2Cl_2 in this way offers little advantage over the use of gaseous chlorine and it has not therefore been generally adopted for laboratory purposes.

A recent example of the application of SO_2Cl_2 in this manner is the work of Jadhav and Sukhtankar on the chlorination of aryl amides of aromatic acids. They have investigated the interaction of SO_2Cl_2 with amides in which the basic constituent is substituted and in which both the acidic and basic constituents are substituted. Chlorination is negligible in the absence of negative substitution groups on the aromatic nucleus. Using variously substituted analogs of benzanilide and equimolar ratios of reactants, they obtained 75-90% yields of monochloro derivatives in which the chlorine entered the basic portion of the molecule in a position <u>para</u> to the amido group. With excess of SO_2Cl_2 a second chlorine atom is introduced into the same nucleus usually in a position <u>ortho</u> to the amido group.

With aryl amides of salicyclic acid as many as four chlorine atoms may be introduced depending on the molar ratios of reactants. Substitution occurs in the following positions in the order named: <u>para</u> to the OH group, <u>para</u> to the NHCOR group, <u>ortho</u> to the OH, <u>ortho</u> to the NHCOR.

In 1936, Reed patented a process for the reaction of paraffin hydrocarbons with a mixture of SO_2 and Cl_2 in which a $-SO_2Cl$ group is introduced into the molecule. This interested Kharasch in the possibility of using SO_2Cl_2 for similar reactions. His investigations have led to the discovery that SO_2Cl_2 may be used as both a chlorinating and a sulfonating agent.

<u>Chlorinations with Sulfuryl Chloride</u>.--Kharasch has found that in the presence of peroxides as catalysts, SO_2Cl_2 can serve as a source of atomic chlorine. Using this procedure it is possible to chlorinate many types of compounds far more readily than is possible by the use of chlorine and light. The compound to be chlorinated is refluxed with SO_2Cl_2 containing a small amount of benzoyl peroxide. Evolution of SO_2 and HCl begins immediately and reaction is complete when no more gases are evolved. The yield is chiefly dependent on the efficiency of the reflux condenser since the gases may carry off some of the volatile reactants. Without special precaution yields of 80% are readily obtained and with care the yield may be made quantitative. The products are isolated by direct fractionation of the reaction mixture.

By this method aliphatic hydrocarbons are readily chlorinated in high yields in a very short time, the degree of chlorination being dependent on the ratio of reactants. Orientation of the entering chlorine atoms is similar to the photochemical chlorination with gaseous chlorine. Secondary hydrogen atoms are more readily substituted than primary and the presence of halogen increases the difficulty of further substitution. This deactivating effect is particularly strong on the carbon atom holding the substituent and decreases with increasing distance from it. The presence of two or more chlorine atoms on a single carbon entirely prevents further substitution. With low boiling compounds the rate of chlorination may be slowed because of the slower decomposition of SO_2Cl_2 at lower temperatures. This may be overcome by use of less stable peroxides, e.g. lauroyl peroxide or by addition of a higher boiling solvent.

Aromatic hydrocarbon sidechains are also readily chlorinated by this method. In the case of toluene, benzyl chloride and benzal chloride are formed depending on the relative amount of SO_2Cl_2 used. Benzal chloride cannot, however, be further substituted. Derivatives and homologs of toluene also react readily chlorinating chiefly on the alpha carbon atom although a small amount of beta substituent is obtained. β-Chloro-tert.-butyl benzene is formed in 70% yields, no alpha position being available. Sidechains of even more reactive nuclei, e.g., m-xylene may be chlorinated without nuclear substitution. However, fluorene and β-methyl naphthalene nuclei are so reactive that nuclear chlorination occurs even in the absence of peroxide. Nitro substitution in the nucleus inhibits sidechain chlorination.

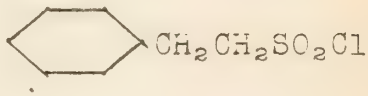
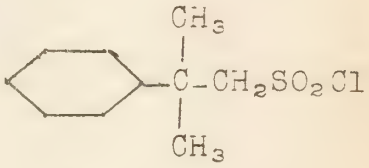
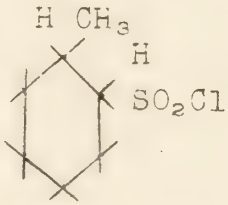
Olefins were known to react with SO_2Cl_2 chlorinating the double bond in the usual manner. On investigation Kharasch found that carefully purified compounds did not react in the absence of peroxides and concluded that previously reported reactions were due to the presence of peroxide impurities in the olefin. The reaction with olefins in the presence of peroxidic substances (benzaldehyde, ascaridole, etc.) is rapid and yields of 80-95% are obtained. Cyclohexene, allyl chloride, stilbene, di- and tetrachloroethylenes and tetraphenyl ethylene have been studied, all forming the corresponding dichlorides.

In all of these chlorinations it was noted that the reactions had the characteristics typical to chain reactions. Also they are similar to photochemical reactions with chlorine gas which is believed to be of the chain mechanism type. Consequently a chain reaction involving free radical intermediates (Cl and SO_2Cl) is postulated.

The reaction of SO_2Cl_2 with acids, aldehydes and ketones is also being investigated and the results are to be reported later.

Sulfonation with Sulfuryl Chloride.--SO_2Cl_2 has been occasionally used to sulfonate aromatic nuclei in the presence of $AlCl_3$. If the free radical mechanism postulated for chlorination is correct then sulfonation through the action of the SO_2Cl radical should also be possible. This possibility has been studied by Kharasch and he has found sulfonation to occur in fair yields. Peroxides cause only chlorination, but by use of aromatic nitrogen ring compounds, e.g., pyridine or quinoli as a catalyst and in the pres-

ence of light, both chlorination and sulfonation occur. As in chlorination the radical reacts with aliphatic hydrocarbons and with aromatic sidechains rather than with the aromatic nucleus. The optimum conditions involve, beside the catalyst, strong illumination, a low concentration of SO_2Cl_2 at any one time, and a temperature of 70° (since above this temperature the dissociation to SO_2 and Cl_2 is considerable and chlorination is increased). The following table lists the results obtained with several types of hydrocarbons.

Hydrocarbon	Catalyst	% Yields Chlorination	% Yields Sulfonation	Sulfonated Product
Ethyl benzene	quinoline	74.6	12.4	
Benzene	pyridine	12.0	--	---
n-Heptane	quinoline	56.0	31.0	$CH_3(CH_2)_6SO_2Cl$
tert.-Butyl benzene	pyridine	22.0	39.0	
Methyl cyclo-hexane	pyridine	21.0	44.0	

This appears to be a general method for aliphatic hydrocarbons and may be extended to alkyl halides and other types of molecules.

Binkley and Degering have recently used SO_2Cl_2 in the preparation of esters of chlorosulfonic acid, by reaction of SO_2Cl_2 in the cold with alcohols, a method first proposed by Busnong. From the corresponding alcohols have been prepared the methyl, ethyl, n-propyl and n-butyl esters all in about 50% yields.

In addition they have extended the reaction to the preparation of dialkylamine sulfuryl chlorides by slow addition of the dialkylamine to SO_2Cl_2 while cooling, followed by a twenty-four-hour reflux. The dimethyl, diethyl, di-n-propyl and di-n-butyl sulfuryl chlorides have been prepared.

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Reported by J. R. Cummings
March 27, 1940

ADDITION AND POLYMERIZATION PRODUCTS OF ACETYLENE

Acetylene has been used for the preparation of acetaldehyde, ketones, polymerization products and resins for many years. Within the last ten years, since the discovery of chloroprene and synthetic rubber, acetylene has reached greater importance industrially. The following table lists some of the substances which are obtained from acetylene.

In presence of	Product	Use
HgO, H_2SO_4, H_2O, 92°	acetaldehyde	preparation of acetic acid, ethyl acetate, acetic anhydride
HgO, $HOAc$(1 mole), SO_3, 50-60°	vinyl acetate	vinyl acetate and "vinylite" resins
HgO, $HOAc$(2 moles), SO_3, 70-90°	ethylidene diacetate	preparation of acetic anhydride, vinyl acetate
Cu_2Cl_2, NH_4Cl, HCl, 80-85°	vinyl chloride	resins and polymers
Cu_2Cl_2, NH_4Cl(2 moles), 65°	vinyl acetylene	preparation of chloroprene, styrene, butadiene
steam	acetone	
NH_3, water-free FeO, 400°	acetonitrile, picoline	
HNO_3(very dil.), HgO	oxalic acid	
H_2SO_4, $HgSO_4$, $MeOH$ (press.) 150°	dimethyl acetal	solvent for cellulose derivatives
$AlCl_3$, $AsCl_3$	Lewisite ($ClCH{=}CHAsCl_2$)	
$NaOH$ (press.)	sodium acetate	
press., Ni catalyst	gasoline of naphthenic hydrocarbons	
C_6H_6	dimethyldihydroanthracene	
$C_6H_5NH_2$, Cu_2Cl_2	quinaldine	dyes
iron sulfide or pyrites	CS_2	
H_2SO_4, HgO, H_2O, phenol	methyl bakelite type resins	
red hot tube, 650°, Si + Cr	benzene, naphthalene, etc.	
thermal decomposition	acetylene black	dry cells, case-hardening, filler for rubber tires

Among the many by-products of these processes are diacetyl (from purification of acetic acid), acetonyl acetone, dimethyl furane, dihydro-p-tolualdehyde (from acetaldehyde residues), and 1,3-butyleneglycoldiacetate.

Hydration of acetylene to acetaldehyde in the presence of salts of Hg and H_2SO_4 is well known and a discussion of this reaction will be omitted. Other alkyne hydrocarbons may be hydrated under similar conditions to the corresponding ketone. Thus methyl ethyl ketone is obtained from vinyl acetylene. More recently Schaad and Ipatieff have demonstrated the use of a solid phosphoric acid containing catalyst for conversion of acetylene and steam to acetaldehyde at 260-300°C. Likewise alkylacetylenes yield the corresponding ketones but at a temperature of 150-200°C. The yield for acetylene amounts to 70 per cent of theoretical using fresh catalyst; the yields of ketones obtained are not reported.

Vinyl acetate and ethylidine diacetate are prepared from acetylene and glacial acetic acid. The catalyst required is made by passing SO_3 into a glacial acetic acid solution of HgO at 40-50°C. The most suitable conditions employ 2.5 per cent HgO and 1-2 per cent excess of precipitant to increase the reaction speed and per cent conversion. The two most important factors governing the ratio of vinyl acetate to the ethylidene acetate produced are vinyl acetate removal and the temperature conditions during the run. The yield of vinyl acetate can be increased to 75 per cent if the reaction temperature is lowered to 50-60°C. and the product removed as rapidly as it is formed. By allowing acetylene to remain in contact with the catalyst a longer time, and carrying out the reaction at 70-90°C., the percentage conversion to ethylidene diacetate, based on acetylene, amounts to 85-90 per cent.

$$C_2H_2 + CH_3COOH \longrightarrow CH_2{=}CHOCOCH_3 \qquad (1)$$

vinyl acetate

$$CH_2{=}CHOCOCH_3 + CH_3COOH \longrightarrow CH_3CH(OCOCH_3)_2 \qquad (2)$$

ethylidene diacetate

If 100 per cent orthophosphoric acid replaces sulfur trioxide as the precipitating agent, acetic acid, reacted with acetylene, can be converted almost quantitatively into vinyl acetate. The optimum temperature in this case is 70-75°C. Meta- and pyrophosphoric acids give high yields of ethylidene diacetate.

Vinyl acetate can also be prepared in the vapor phase by employing a nine-fold excess of acetylene, a temperature of 180-250°C., and a catalyst of Cd and Zn acetates on activated carbon.

The main use for ethylidene diacetate is in the preparation of acetic anhydride. When the ester is heated at 70-80°C. with sulfuric acid as catalyst under 100 mm. pressure, the resultant mixture contains acetic anhydride and paraldehyde (German Patent, 1923). Morrison and Shaw state that, in the presence of a catalyst (SO_2 or SO_3), the decomposition of ethylidene diacetate is rapid above 150°C. giving chiefly acetic anhydride and acetaldehyde with some vinyl acetate and acetic acid.

Vinylacetylene and divinylacetylene are prepared from acetylene in the presence of a catalyst of CuCl and NH_4Cl. Divinylacetylene is best made by absorbing acetylene in the catalyst solution and aging the mixture for five to seven days after which the products of polymerization are distilled. The yield of divnylacetylene is 70-80 per cent and of a tetramer is 10 per cent. Distillation of the mixture immediately after saturation with acetylene results chiefly in monovinyl acetylene.

$$CH{\equiv}CH + HC{\equiv}CH \longrightarrow \underset{\text{monovinylacetylene}}{CH_2{=}CH{-}C{\equiv}CH}$$

$$CH_2{=}CH{-}C{\equiv}C{-}H + HC{\equiv}CH \longrightarrow \underset{\text{divinylacetylene}}{CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH_2}$$

$$CH_2{=}CH{-}C{\equiv}CH + HC{\equiv}C{-}CH{=}CH_2 \longrightarrow \underset{\text{tetramer}}{CH_2{=}CH{-}CH{=}CH{-}C{\equiv}C{-}CH{=}CH_2}$$

The yield of monovinylacetylene is affected by the concentration of catalyst, depth of catalyst solution, temperature, amount of contact of acetylene and catalyst. Hurukawa and Nakamura have found:

1. Best yields were obtzined with a $CuCl:NH_4Cl$ ratio of 1:1 mole and $CuCl:H_2O$ ratio of 1:1 by weight. About 3 per cent of HCl was necessary although higher concentration resulted in the formation chiefly of vinyl chloride and acetaldehyde.

2. Highest yields of monovinylacetylene were obtained at 65° C. A higher temperature produced acetaldehyde and divinylacetylene.

3. It was very difficult to disperse acetylene in the catalyst solution.

4. Maximum yield of monovinylacetylene was 44.5 per cent and 30 per cent acetylene was converted. The low yield is explained not by chemical conditions but rather by poor physical conditions.

5. Monovinylacetylene was best recovered by absorption in a suitable liquid such as xylene.

Hurukawa and Nakamura give the following as optimum conditions for the discontinuous preparation of chloroprene upon addition of hydrochloric acid to monovinylacetylene:

reaction temperature - 25-30°
concentration of HCl - 36.5 per cent
reaction time - 1-5 hours in excess HCl

They contend that a continuous process is not applicable because chloroprene reacts with more hydrochloric acid forming large quantities of the dichloride.

Klebanskii, however, claims that in the presence of a large excess of hydrochloric acid or an excessively long duration of the reaction (over five minutes) or at temperatures above 20° C., the reaction proceeds further with formation of 2,4-dichloro-2-butene.

$$CH_2{=}CH{-}C{\equiv}CH + HCl \longrightarrow ClCH_2{-}CH{=}C{=}CH_2 \qquad (1)$$

$$ClCH_2{-}CH{=}C{=}CH_2 \longrightarrow CH_2{=}CCl{-}CH{=}CH_2 \qquad (2)$$

$$CH_2{=}CCl{-}CH{=}CH_2 + HCl \longrightarrow CH_3{-}CCl{=}CH{-}CH_2Cl \qquad (3)$$

The isomerization of 4-chloro-1,2-butadiene to chloroprene proceeds best of all by the action of dilute hydrochloric acid in the presence of the catalyst, $CuCl{\cdot}NH_4Cl$. To prevent formation of the dichloride, then, the catalyst solution is added with energetic stirring to monovinylacetylene at 0°C., slightly below the boiling point of this reactant.

Trenke has developed a continuous process for polymerization and hydrochlorination of acetylene in one stage in which the gaseous phases are reacted in a tower type apparatus. Under definite conditions of optimum procedure (concentration of HCl about 25-27 per cent, of catalyst 10-12 per cent of CuCl, and temperature 20°C.) the addition of hydrochloric acid to vinylacetylene only and none to acetylene takes place. The yield of chloroprene under these conditions reaches 80 per cent and higher.

Oxalic acid can be prepared by passing acetylene into nitric acid containing silver nitrate under the following conditions:

1. The acetylene contains 10 per cent oxygen
2. The reaction temperature is 10°C.
3. The initial HNO_3 concentration is 55 per cent
4. $AgNO_3$ concentration is 2 g./100 cc. of HNO_3
5. Velocity of gas is 8 l./hr.

Vinyl chloride was prepared from acetylene and hydrochloric acid employing a catalyst of CuCl and NH_4Cl under the following conditions:

Concentration of CuCl - 23 per cent
Concentration of NH_4Cl - 16 per cent
Concentration of HCl - 15.5 per cent
Concentration of H_2O - 45.5 per cent
Temperature - 30-85°C.

The yield of vinyl chloride was 26 per cent of the acetylene passed. Increase in temperature and amount of catalyst increased the velocity of reaction. If $CaCl_2$ replaces NH_4Cl, a temperature 65° must be used.

Toussaint passed acetylene and dry HCl into a suspension of $HgCl_2$ in anhydrous $SnCl_4$ at 55° and recovered vinyl chloride. Acetylene combines directly with HCl over activated carbon at 100-130° if Hg is present as a catalyst.

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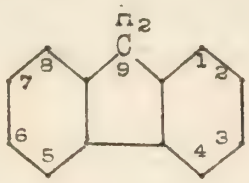
Reported by R. G. Handrick
April 3, 1940

THE STRUCTURE AND REACTIONS OF FLUORENE

Bergman and Berlin, Daniel Sieff Research Institute
Lothrop--Trinity College

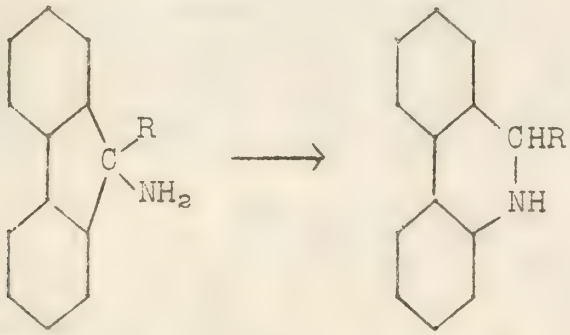
Although fluorene was discovered in 1867, it has not been as widely studied as other similar hydrocarbons, because there has been no practical problem dependent upon its nature, as in the case of anthracene and phenanthrene. Berthelot isolated fluorene from crude anthracene and distinguished it from other hydrocarbons by its physical properties and by an elementary analysis. A formula (I) was assigned to it when its oxidation product was found to be identical to the biphenylene ketone which had been characterized by Fittig.



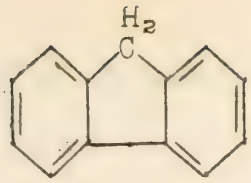
There is no undisputed space formula for the molecule, but x-ray and dipole moment measurements support the theory which seems to be the accepted one. It seems likely that the five-membered ring is regular, or nearly so, each angle being 108°. Then, if each angle in the benzene rings is to be 120°, the rings must be distorted about 12-13° from the plane of the diphenyl molecule, if the molecule is to remain planar.

The fact that fluorenone 9-carboxylic acid does not close a fourth ring has been used as proof of this planar structure, since it indicates that the distance has become too great to be bridged.

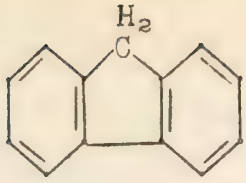
There will be a large amount of strain involved in going from a diphenyl structure to the fluorene one. That strain is involved is shown by the readiness with which the ring is enlarged by a Stieglitz rearrangement to give a phenanthrene derivative.



Part of the strain is compensated by the inclination of the two rings and it is also partially relieved by an arrangement of the double bonds according to the Mills-Nixon effect (III).

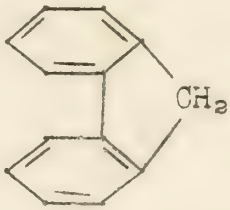


III

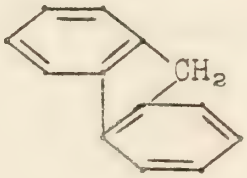


IV

If there is to be distortion, with the planes inclined, there should be stereoisomers, and two 9-aminofluorenes were reported. Kuhn and Jacob postulated a folded structure to explain these, but it was disproved on the same grounds as Kaufler's formula for diphenyl.



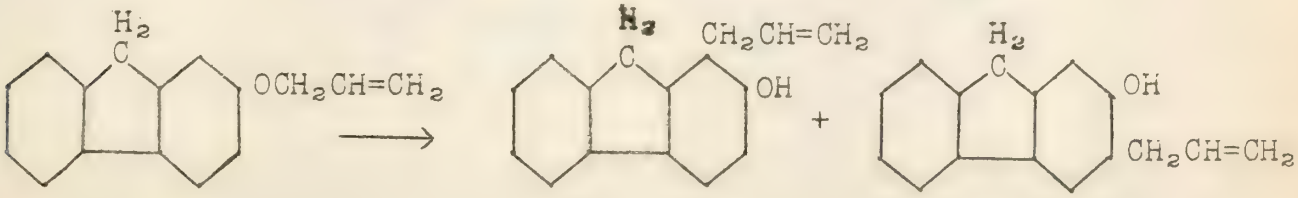
and



It was later shown that actually only one 9-aminofluorene exists. If isomers are to exist, it would mean that the two hydrogens in the nine position are different. However, attempts to resolve unsymmetrically substituted fluorenes have failed, leaving doubt still as to the existence of stereoisomers.

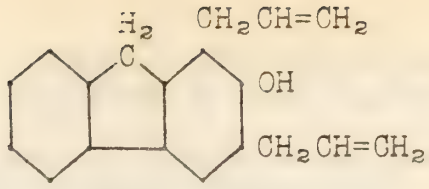
There are two possible positions of the double bonds in fluorene (III and IV). The evidence for III depends upon ring closures in the three position of γ-2-fluoryl butyric and o-(2-fluoryl) benzoic acids which places the double bonds between 2 and 3. IV is naphthalenic, and it is supported by refractive studies and by the quinone-like properties of fluorenone. It is disputed on the basis of the special reactivity of the two and seven positions, which would correspond to the 4-4' in diphenyl.

Lothrop has applied methods used on naphthalene and benzene to determine whether or not there is a frozen structure. With β-naphthol, the allyl ether will rearrange smoothly to the one position, and the -OH will couple at C, with $C_6H_5N_2Cl$, but neither rearrangement will work if the one position is filled. He prepared the allyl ether of 2-hydroxyfluorene, and on pyrolysis obtained two compounds. Pyrolysis of the allyl ethers of these gave only one compound.



VI VII

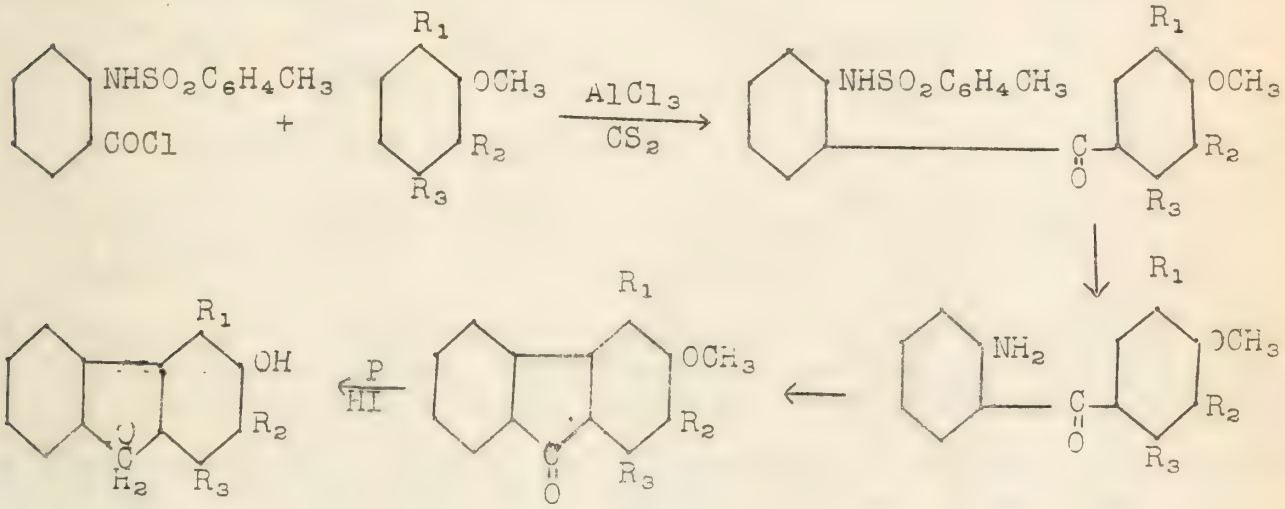
Allyl ethers of VI and VII $\xrightarrow{\Delta}$



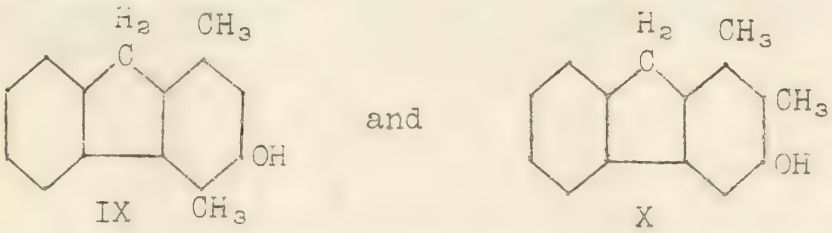
VIII

Such a reaction would be impossible with a fixed structure, which would indicate a benzenoid rather than a naphthoid configuration. Pyrolysis of a similar 3-hydroxy compound yielded a useless gum.

To establish the chemical reactivity of the hydroxyl in the three position, derivatives were made in which first one ortho position and then the other were covered. They were prepared by a general method:



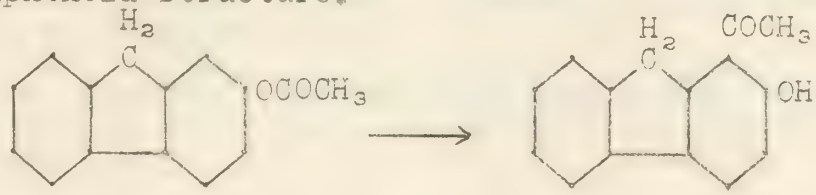
The compounds prepared were:



IX and X

The allyl ethers rearranged smoothly, and the coupling reaction was rapid, pointing to two different positions for the double bonds.

2-Acetoxy fluorene undergoes a Fries rearrangement which would require a naphthoid structure.



2-Acetoxy fluorenone gives 1-acetyl-2-hydroxylfluorenone, the position of the rearranged group being known by the fact that it gives a pyrazidine derivative. 2-Allyloxy fluorenone rearranges to give two isomers in a molecular compound which can be hydrogenated

to give 1-propyl-2-hydroxy- and 3-propyl-2-hydroxyfluorenone. This is only possible with a system of shifting double bonds.

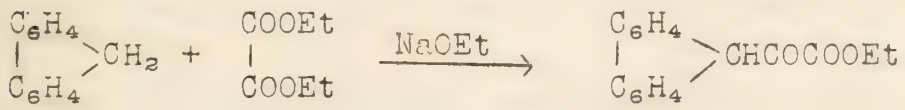
Reactions of Fluorene.--Fluorene contains an active methylene group. Its activity compares with similar compounds:

cyclopentadiene > indene > fluorene.

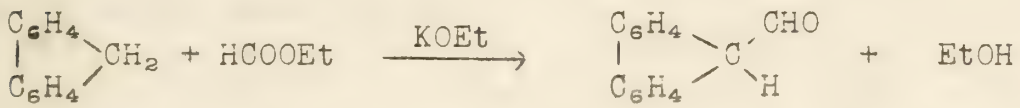
Typical reactions of the fluorene molecule are:

1. Formation of Na and K derivatives.

2. Condensation with ethyl oxalate



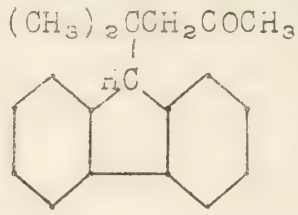
3. Condensation with ethyl formate



4. Condensation with aromatic aldehydes: In the presence of NaOEt it splits out water. This reaction does not go with aliphatic aldehydes or with ketones, under the same experimental conditions.

5. Magnesium derivatives: In the presence of toluene, fluorene will form a Grignard which will undergo the usual reactions.

6. Reaction with acetone: In the presence of powdered KOH, this reaction yields mesityl oxide and a compound $C_{19}H_{20}O$ which has the structure



and showed the reaction to be a Michael-type condensation.

7. Condensation with itself: Two molecules of fluorene in vapor state in the presence of PbO, condense to give dibiphenylene-ethylene, a red hydrocarbon.

8. Oxidation: Fluorene oxidized with SeO_2 gives a small yield (5 per cent) of fluorenone. With $KMnO_4$ the reaction gives a good yield.

9. Fluorenols are made by the reaction of a suitable Grignard on fluorenone or by the reduction of fluorene with aluminum amalgam. Fluorenols may be dehydrated to give alkyl or aryl methylene derivatives.

10. Chloro derivatives are made by the reaction of PCl_5 on fluorene or fluorenone.

11. Substitutions in the benzene ring: Nitration, sulfonation, halogenation, may be carried out in the usual manner. The substituents go first into the two, then the seven position.

12. 9-Aminofluorene is made by reducing the oxime of fluorenone. Treatment of the oxime with HgO for eighteen hours yields diazofluorene.

13. Reduction: Fluorene can be reduced with P + HI + heat, producing the octa- and decahydrofluorene. $C_{13}H_{16}$, hexahydrofluorene is found in certain coals and may be dehydrogenated. The position of the remaining double bonds in these is not certain.

Derivatives of fluorene are most easily synthesized from suitably substituted phenanthraquinones, by Friedel-Crafts reactions, or by ring closures involving suitable biphenyls. Few are made by direct substitution.

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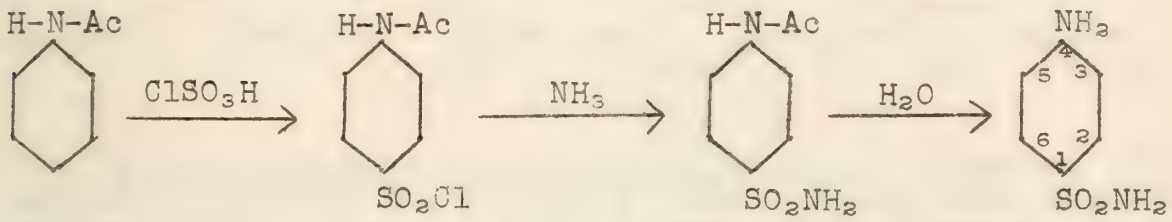
Reported by Elizabeth L. Weston
April 3, 1940.

SULFANILAMIDE AND DERIVATIVES

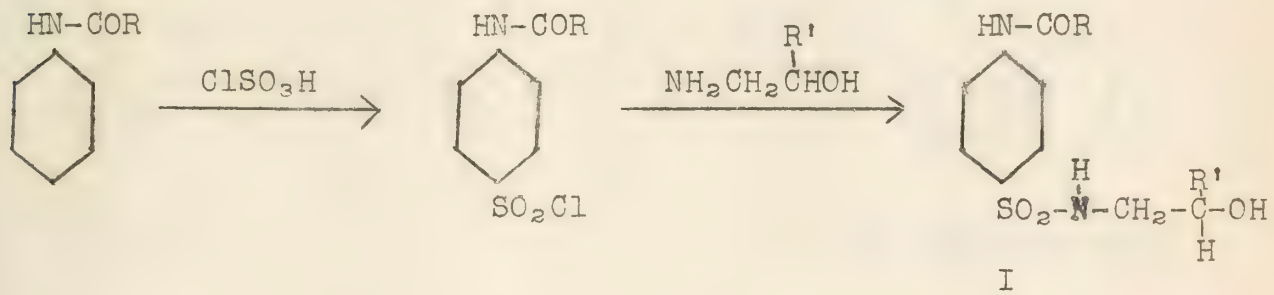
Sulfanilamide was first synthesized by P. Gelmo as a dye intermediate in 1908. Many other dye intermediates containing the sulfanilamide group have been synthesized since azosulfanilamide compounds have great fastness as dyes. Domagk was the first to report the use of Prontosil in the treatment of streptococcal infections in mice and rabbits. In 1935 Nitti, Bovet and coworkers discovered that the azo linkage of Prontosil was broken in the animal body to yield sulfanilamide. These investigators found that sulfanilamide possessed higher activity than Prontosil. This discovery has led to the preparation of a great number of sulfanilamide derivatives during the past five years.

Methods of Preparation.--



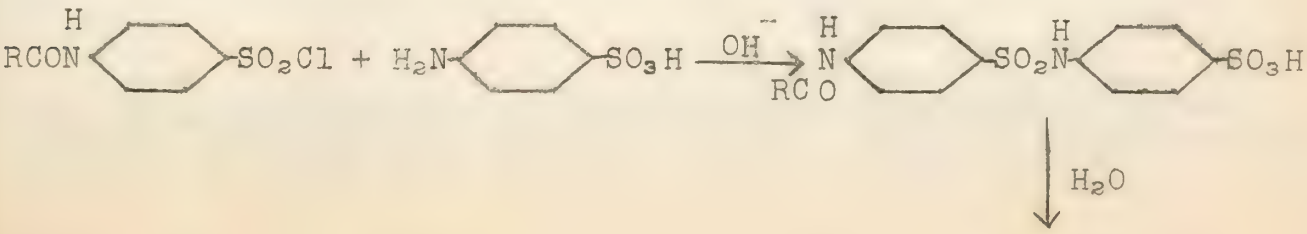
sulfanilamide

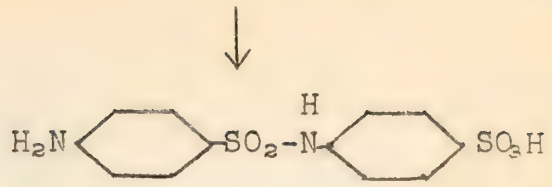
When other N-acyl derivatives are desired, the starting compound may be the corresponding anilide. Stewart's method is used to obtain the p-acyl amido benzene sulfonyl chloride. The latter will react with ammonia or any desired amine to give the substituted benzene sulfonamide:



Compound I may be esterified with a long-chain aliphatic acid in order to give the compound greater lipoid solubility.

Sulfanilyl Derivatives.--To prepare these, N^4-amido benzene sulfonyl chloride is made to react with sulfanilic acid and its derivatives:

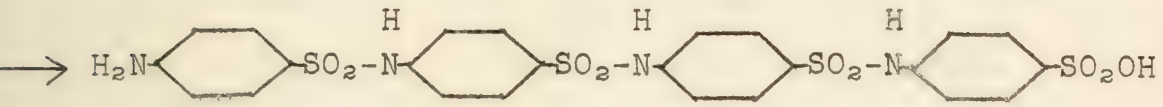




II

The sodium salt of II has greater solubility than sulfanilamide itself, but has only one-third of its therapeutic activity.

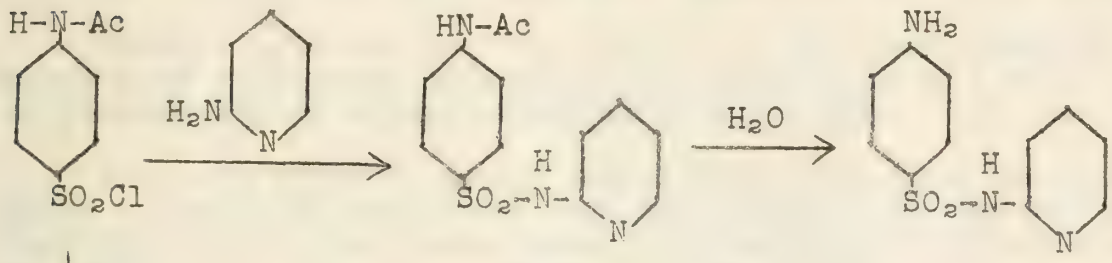
This reaction may be used to form a linear chain of sulfanilyl units:



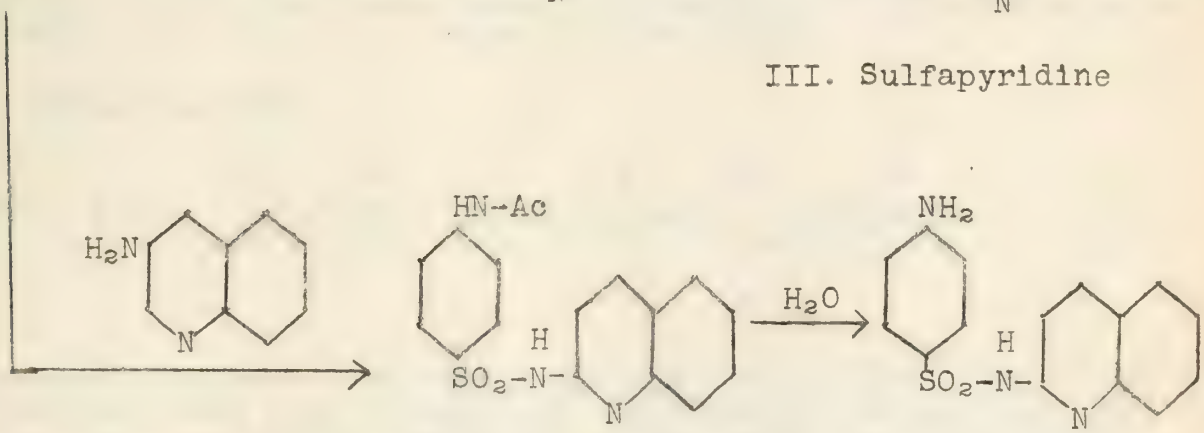
III

Strepto-N-trisulfanilyl Sulfanilic Acid.--Compound III forms emulsions in water and possesses greater therapeutic activity than sulfanilamide. Thus, it would appear that an increase in the number of sulfanilyl units brings about a corresponding increase of activity.

Sulfanilyl Derivatives of Pyridine and Quinoline Amines.--

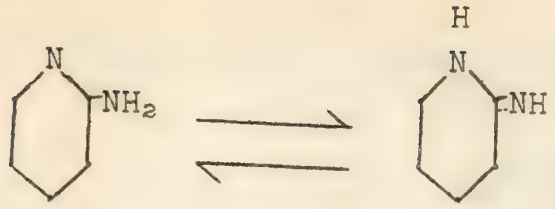


III. Sulfapyridine

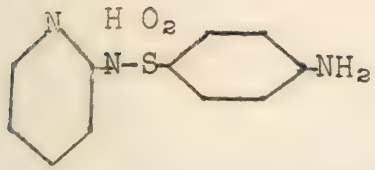


IV

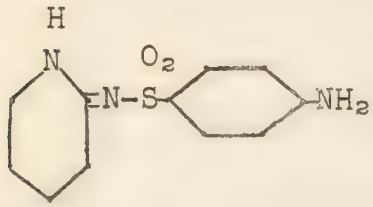
Proof of Structure of Sulfapyridine.--2-Aminopyridine can exist in two tautomeric forms (V and VI). Thus, sulfapyridine may have one of three possible structures (VII, VIII, or IX).



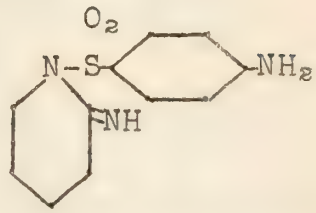
V VI



VII



VIII



IX

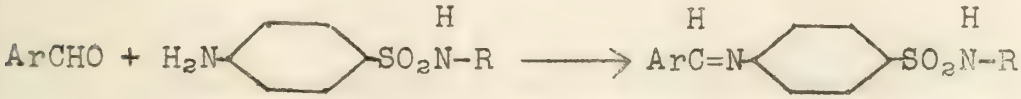
2-Aminopyridine (VI) undergoes hydrolysis in boiling sodium hydroxide with evolution of ammonia and the production of pyridone. Actually no hydrolysis of 2-sulfanilamido pyridine occurs upon boiling the compound with 50 per cent sodium hydroxide.

Upon boiling with 36 per cent hydrochloric acid quantitative yields of sulfanilic acid are obtained. This evidence supports structure VII and is against VIII and IX.

Further evidence for VII exists in that this compound forms a monosodium salt which hydrolyzes in water to give a Ph of 11. This is characteristic of sulfonamides of this type.

While VIII and IX might conceivably give rise to monosodium salts it would be predicted from the behavior of the sodium salt of 2-aminopyridine that these would be more highly hydrolyzed in water and would give rise to a higher Ph than found.

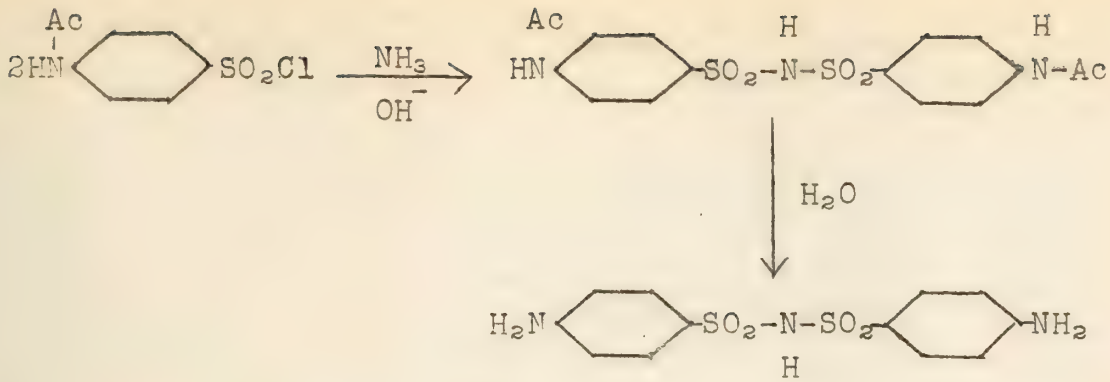
<u>Schiff's Bases</u>.--



X

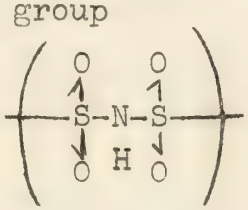
These condensations give nearly quantitative yields. Many arylidine derivatives have been prepared in this manner. These compounds are not as toxic as sulfanilamide but have a much lower therapeutic activity.

Other types of condensations have been used to prepare polynuclear derivatives:



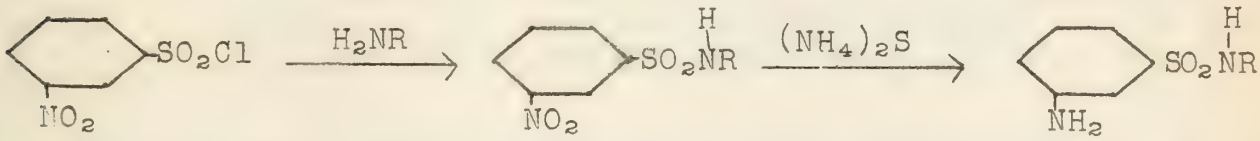
disulfanilamide XI

Disulfanilamide possesses interesting physical and physiological properties. The group



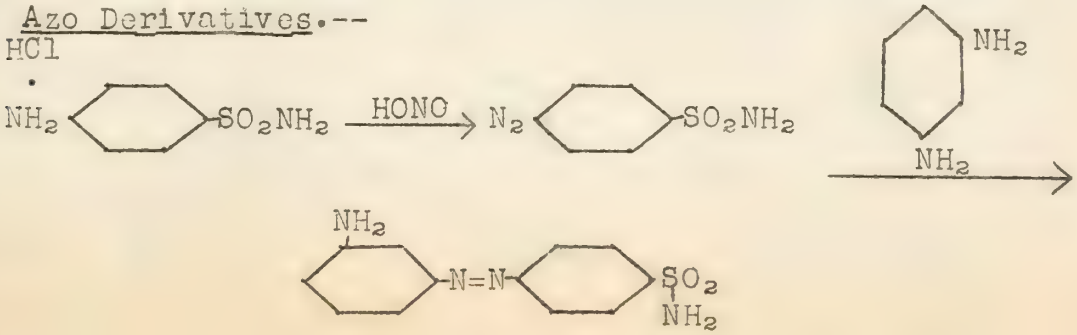
has strong acidic properties and forms a neutral sodium, water-soluble salt. Disulfanilamide has been alkylated but the alkyl derivatives are only slightly water soluble. Both the sodium salt and the methyl derivative have greater activity than sulfanilamide.

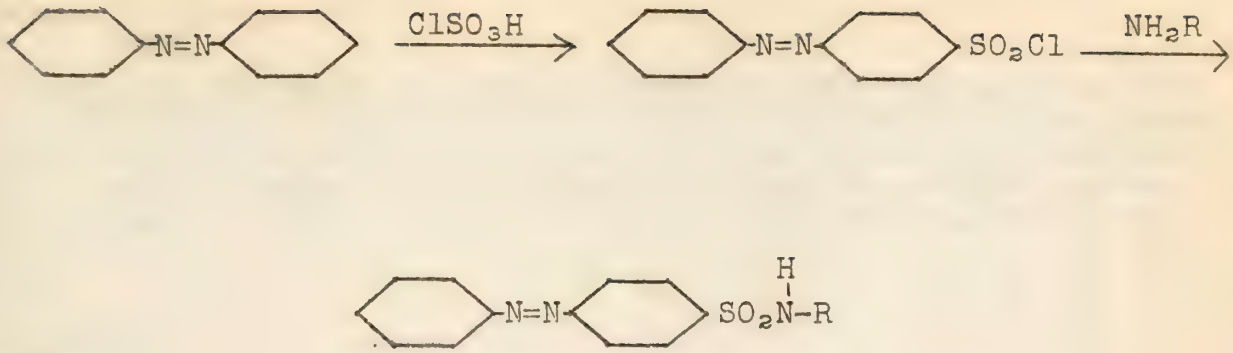
Ortho-and Metanilyl Derivatives.--In the preparation of these, the corresponding nitro derivatives of benzene sulfonyl chloride are made to condense with the appropriate amine and the nitro group is then reduced by ammonium polysulfide.



Ortho-and metanilyl derivatives have been found inferior to sulfanilamide in activity.

Azo Derivatives.--

1. 

2. 

Many studies by Fourneau, Adams, Rosenthal, Crossley and others have been undertaken to relate chemical structure to therapeutic activity in these compounds.

The following generalities are indicated:

1. Little or no activity is found in mononuclear compounds in which either the amino or sulfonamide groups are replaced.

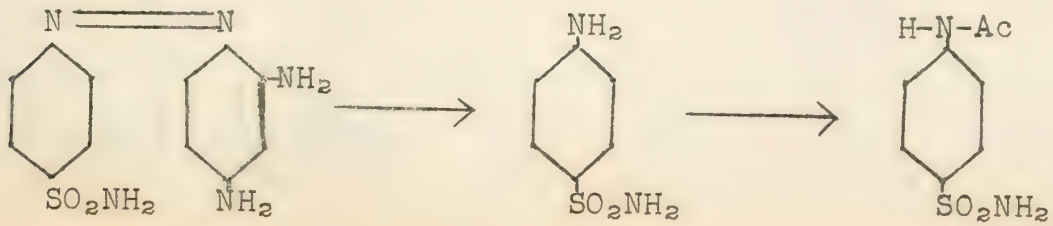
2. Shifting the amino group to o- or m-position results in marked loss of activity.

3. A third group upon the ring lowers the activity.

4. Substitution of the amino group with alkyl, aralkyl, substituted alkyl or aryl, acyl or alkylidene groups has little effect but in general lowers the activity.

5. Substitution of the amido "N" has a variable effect. Methyl and ethyl groups do not change the activity, while higher alkyl groups decrease the activity, p-Amino- and p-nitrophenyl groups increase the activity. When amino alcohols, amino acids, esters and morpholine are condensed, the resulting derivatives appear to be almost inactive, while the difurfuryl amine is toxic.

Reactions of Sulfanilamide and Related Compounds in the Animal Organism.--In the mouse, rat, cat, rabbit, monkey, and man sulfanilamide is conjugated with acetic acid and is excreted as the N^4-acetyl derivative. This is a detoxicating mechanism since it has been found that N^4-acetyl derivatives are much less toxic than sulfanilamide itself. Azo derivatives such as Prontosil are broken in the animal organism to yield sulfanilamide which is then detoxicated as above.



Prontosil

Method of Analysis of Sulfanilamide in Body Fluids.--The most widely used method is that of E. K. Marshall in which sulfanilamide is first diazotized with nitrous acid and the resulting diazo compound is coupled with dimethyl α-naphthylamine to produce a purplish red azo dye which is easily estimated by colorimetric comparison..

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Reported by M. Witte
April 10, 1940.

DIKETENE

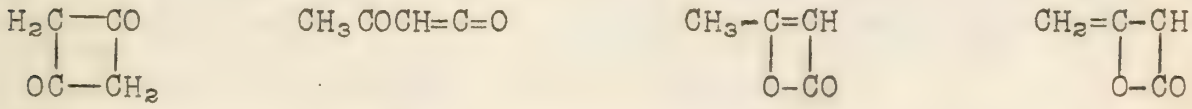
A. B. Boese, Jr., Mellon Institute

Compared to the majority of aliphatic chemicals introduced to industry in recent years diketene is a relatively new compound; it was discovered about thirty years ago. The synthesis of other compounds from diketene has not been commercially important in the past because of the difficulty of preparing diketene in large quantities. Within the last year diketene has become commercially available; therefore, its conversion into derivatives commercially useful should assume considerable importance in the future.

The patented process for producing diketene involves the dimerization of ketene. Usually the ketene, formed by pyrolysis of acetone, is passed into some previously formed diketene. The temperature is maintained at 0-50° and pressure may be used. A small proportion of a mineral acid or acetyl chloride may be added to catalyze the reaction.

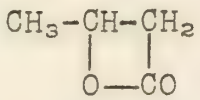
Diketene is a colorless, nonhydroscopic liquid, insoluble in water but soluble in the common organic liquids inert toward it. It has an intensely pungent odor and its vapors are extremely lachrymatory. It is very stable around 0°, but polymerizes slowly on standing at room temperature.

Four structural formulas have at various times been proposed for diketene.



I II III IV

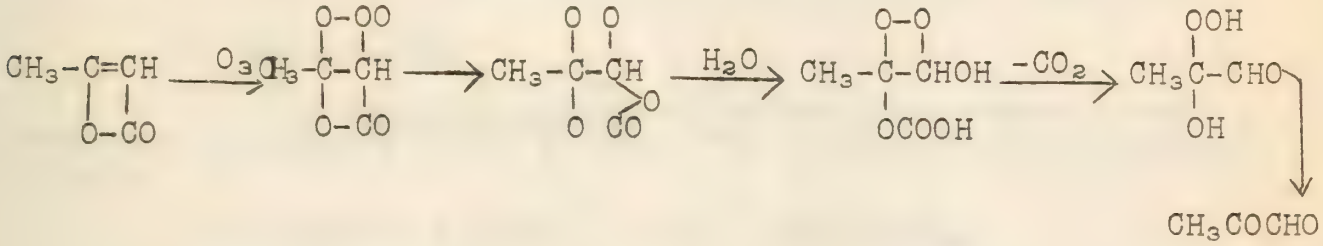
Formula I, cyclobutane-1,3-dione, was proposed by Chick and Wilsmore. It explains (1) the relative inertness of diketene to alcohols, (2) the reaction of bromine to give γ-bromoacetoacetyl bromide exclusively. However, it does not explain (1) reaction of ozone to give pyruvic aldehyde, CH_3COCHO (the compound $OHCCOCH_2COOH$ would be expected), (2) hydrogenation to yield β-butyrolactone



and (3) the reaction of chlorine at low temperatures to give α-chloroacetoacetyl chloride.

Formula II, acetylketene, was also proposed by Chick and Wilsmore. It explains (1) the reaction of diketene with water to give acetoacetic acid, (2) the reaction of barium hydroxide to give barium acetate, (3) the reaction with aniline to give acetoacetanilide, (4) formation of pyruvic aldehyde by ozonolysis, and (5) the product of chlorination. However, it does not explain the product of bromination.

Formula III, β-crotonolactone, which is a resonance isomer of acetylketene, was proposed by Hurd. It explains (1) the relative inertness of diketene to water and alcohols, (2) the results of hydrogenation, and (3) the formation of pyruvic aldehyde on ozonolysis according to the following mechanism.



However, it does not explain (1) the exclusive formation of γ-bromoacetoacetyl bromide on bromination, and (2) the product of chlorination.

Formula IV, vinylaceto-β-lactone, was proposed by Wilson. It explains (1) the relative inertness of diketene to water and alcohols, (2) the addition reactions, and (3) the results of bromination and hydrogenation. However, it does not account for (1) the formation of pyruvic aldehyde on ozonolysis, and (2) the product of chlorination.

The author prefers the vinylaceto-β-lactone structure. However, acetylketene (formula II) appears the most satisfactory to account for mostof the reactions of diketene and will be used to illustrate the reactions given in this paper.

A summary of the more important reactions of diketene, together with the potential use of some of the products will be given in the following pages.

1. <u>With water</u>.--Diketene reacts with water in the presence of a catalyst to give acetoacetic acid which, in turn, decomposes into acetone and carbon dioxide.

$$CH_3COCH{=}C{=}O + H_2O \xrightarrow{H^+} CH_3COCH_2COOH \longrightarrow CH_3COCH_3 + CO_2$$

With pure water in the absence of a catalyst the reaction is quite slow even at elevated temperatures.

2. <u>With alcohols</u>.--Diketene and alcohols in the presence of an acid catalyst react to yield the corresponding esters of acetoacetic acid.

$$CH_3COCH{=}C{=}O + ROH \xrightarrow{H^+} CH_3COCH_2COOR$$

By this method ethyl acetoacetate can be produced in commercial quantities more easily and economically than by the classical sodium condensation of ethyl acetate. The reaction is an extremely general one and is applicable to all aliphatic alcohols from primary to

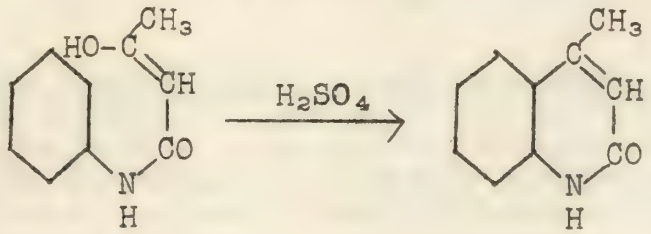
tertiary, alcohol ethers, chlorohydrins, substituted alcohols, glycols, glycerol, and phenols. The acetoacetic esters are useful as solvents for lacquers and other surface coatings, and those of higher molecular weight may be of value as plasticizers. Certain of their metallic salts have shown promise as resin stabilizers.

3. With amines.--

(a) Aromatic amines.--Diketene and primary aromatic mono- and polyamines react to yield the corresponding acetoacetyl amines.

$$CH_3COCH{=}C{=}O + ArNH_2 \longrightarrow CH_3COCH_2CONHAr$$

The acetoacetanilides are used as intermediates for the production of Hansa yellow dyes. Diacetoacetyl diamino compounds of the diaryl series are extensively used as developers for producing dyes directly on cotton. Typical examples of this series are N,N'-diacetoacetylbenzidine, $CH_3COCH_2CONHC_6H_4-C_6H_4NHCOCH_2COCH_3$, and N,N'-diacetylaceto-o-toluidine, $CH_3COCH_2CONHC_6H_3(CH_3)-C_6H_3(CH_3)NHCOCH_2COCH_3$. When treated with strong dehydrating agents, such as sulfuric or phosphoric acid, acetoanilides undergo ring closure to form 4-methylcarbostyril and its derivatives.



These compounds have shown activity as corrosion inhibitors and bactericides; their use as intermediates for dyestuffs and pharmaceuticals is also indicated.

(b) Aliphatic amines.--Diketene reacts with aqueous solutions of ammonia and primary and secondary aliphatic amines to form acetoacetamide or nitrogen-substituted acetoacetamides.

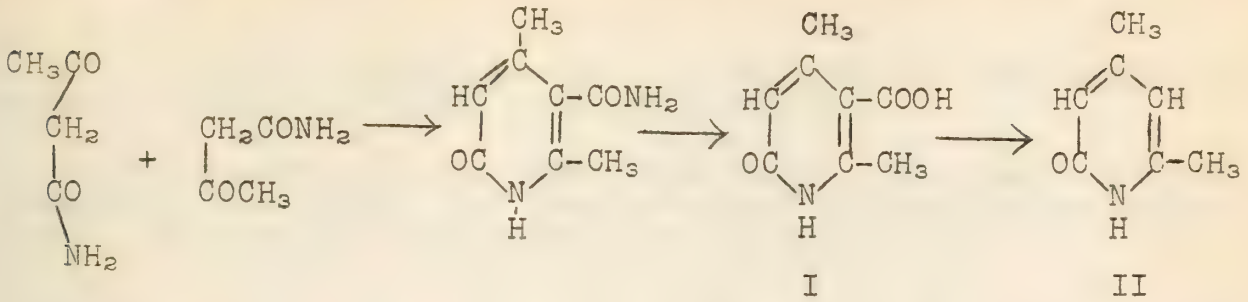
$$CH_3COCH{=}C{=}O + \begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!NH \longrightarrow CH_3COCH_2CON\!<\!\begin{matrix} R_1 \\ R_2 \end{matrix}$$

where R_1 and R_2 = H or alkyl groups

Here is presented a method for preparing acetoacetyl primary and secondary aliphatic amines which have not been described previously in the literature.

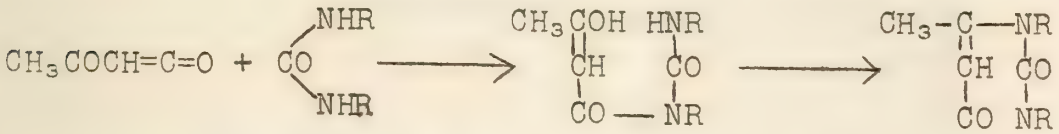
The lower members of the series have indicated value as dye solvents, constituents of wood stains, and as intermediates for the preparation of formaldehyde condensation resins.

When heated, acetoacetamide condenses with itself to form lutidone carboxylic acid (I) and lutidone (II).



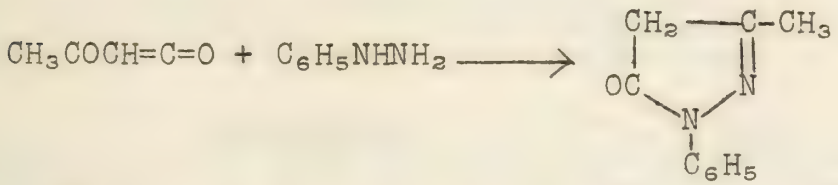
These compounds are of interest as intermediates for further syntheses.

4. <u>With ureas</u>.--Diketene and urea or symmetrically disubstituted ureas react to yield 4-methyluracil or its homologs.



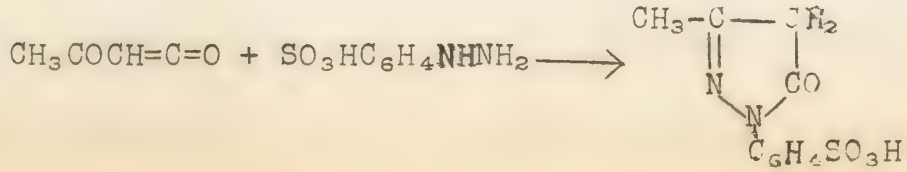
where R = H or an alkyl group.

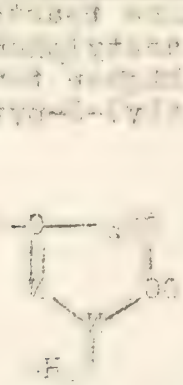
5. <u>With phenylhydrazine and phenylhydrazine sulfonic acid</u>.--At temperatures around 20°, diketene reacts with phenylhydrazine to form the phenylhydrazone of acetoacetylphenylhydrazine, $CH_3C(=NNHC_6H_5)CH_2CONHNHC_6H_5$. If higher temperatures are employed, the reaction yields 1-phenyl-3-methyl-5-pyrazolone in high efficiency.



Phenylmethylpyrazolone and its derivatives are constituents of an important class of azo dyes. Phenylmethylpyrazolone also serves as a starting material in the synthesis of the valuable analgesic "antipyrine."

When diketene is added to an aqueous suspension of phenylhydrazine sulfonic acid, 1-sulfophenyl-3-methyl-5-pyrazolone is formed.

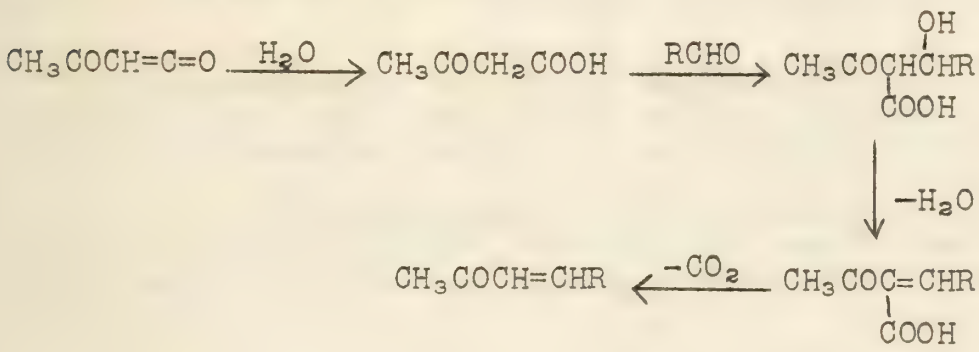




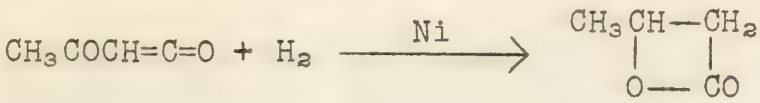
The sulfophenylmethylpyrazoline is an important dye intermediate.

6. With aldehydes.--When heated, formaldehyde and diketone react to form a polymeric resinous material.

With aldehydes higher than formaldehyde, an aldol-type condensation takes place, the final products being α,β-unsaturated ketones. The probable mechanism of this reaction is:



7. Hydrogenation.--When hydrogenated in the liquid phase in the presence of nickel, diketene yields β-butyrolactone, and, in addition, a small amount of butyric acid.



β-Butyrolactone may be readily hydrolyzed to β-hydroxybutyric acid, a compound of pharmaceutical importance and an intermediate for the preparation of a great number of esters and acetyl derivatives useful as solvents and plasticizers.

8. Halogenation.--Diketene, either in the pure state or dissolved in an inert solvent, rapidly absorbs chlorine at low temperatures to yield γ-chloroacetoacetyl chloride, which probably is formed by a rearrangement of the α-chloroacetoacetyl chloride first formed.

$$CH_3COCH{=}C{=}O + Br_2 \longrightarrow CH_3COCHBrCOBr \longrightarrow BrCH_2COCH_2COBr$$

Bromine reacts to yield γ-bromoacetoacetyl bromide.

These chloro- and bromo- compounds are useful as synthetic intermediates.

When treated with water, γ-chloroacetoacetyl chloride gives monochloroacetone.

$$ClCH_2COCH_2COCl + H_2O \longrightarrow ClCH_2COCH_3 + CO_2 + HCl$$

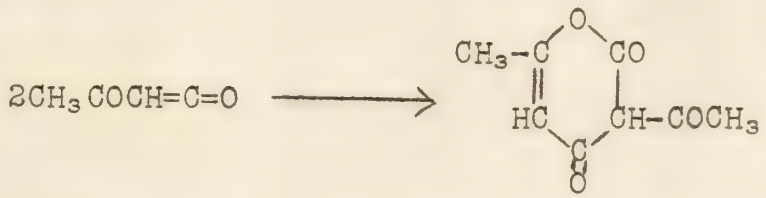
The chloroacetone obtained in this manner is free of higher chlorinated acetones, hence this is a convenient method of preparing monochloroacetone in a pure state. Pure monobromoacetone can be obtained in a like manner.

9. With aromatic hydrocarbons.--Diketene reacts with aromatic hydrocarbons in the presence of aluminum chloride to yield aromatic 1,3-diketones.

$$CH_3COCH{=}C{=}O + C_6H_6 \xrightarrow{AlCl_3} CH_3COCH_2COC_6H_5$$

These diketones are useful as plasticizers, particularly for resins of the vinyl type. Chemically they exhibit all the reactions of 1,3-diketones and are useful as synthetic intermediates.

10. Polymerization.--When diketene is added slowly to an inert solvent at 70-120°, containing a small amount of catalyst, the diketene polymerizes to dehydroacetic acid with a 60-80 per cent yield.



As catalysts, tertiary amines, such as pyridine, triethylamine, and methylmorpholine, and alkali metal salts of hydroxy compounds, such as sodium ethylate and sodium butyrate, have been found most efficient; aromatic hydrocarbons, such as benzene and toluene, are most suitable as solvents.

Dehydroacetic acid is noteworthy for the large number of derivatives into which it may be transformed by the action of acids and bases under varying conditions.

11. Depolymerization.--When diketene vapor is passed through a tube heated to 550-600°, it depolymerizes quantitatively into its monomer, ketene.

$$CH_3COCH{=}C{=}O \xrightarrow{550\text{-}600^\circ} 2CH_2{=}CO$$

Thus, for the first time, a convenient and simple process is available for rapidly producing pure ketene uncontaminated by methane and other hydrocarbons and oxides of carbon.

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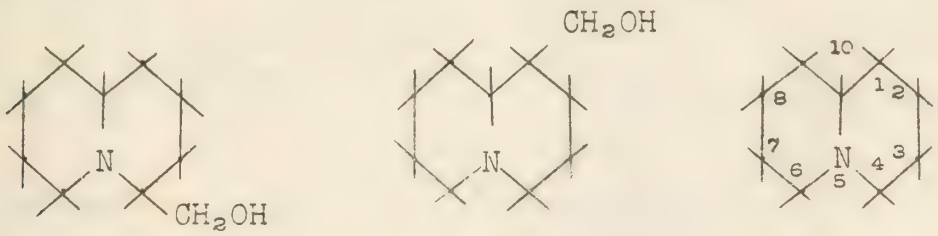
Reported by L. B. Poland
April 10, 1940.

THE SYNTHESIS OF THE ALKALOID ALLOLUPININE

Winterfeld and Holschneider -- Pharmazeutisches
Institut der Universität Freiburg i. Br.

The lupine alkaloids are derivatives of the parent substance norlupinane (III). The lupine group consists of lupinine (II) and sparteine ($C_{15}H_{26}N_2$) which are the most important and also lupanine ($C_{15}H_{24}ON_2$), anagyrine ($C_{15}H_{20}ON_2$), monolupine ($C_{16}H_{22}ON_2$), cytisine ($C_{11}H_{14}ON_2$) and matrine. A structure has been proposed for sparteine but not much is known about the last five named.

Sparteine is found most abundantly in the common broom, Spartium scoparium. Lupinine, the most important in the group, is found in the seeds of yellow lupine, Lupinus luteus, which grows in the Mediterranean region and in North and South America, being most abundant in the western states. These alkaloids have been known for several decades and are mild poisons.



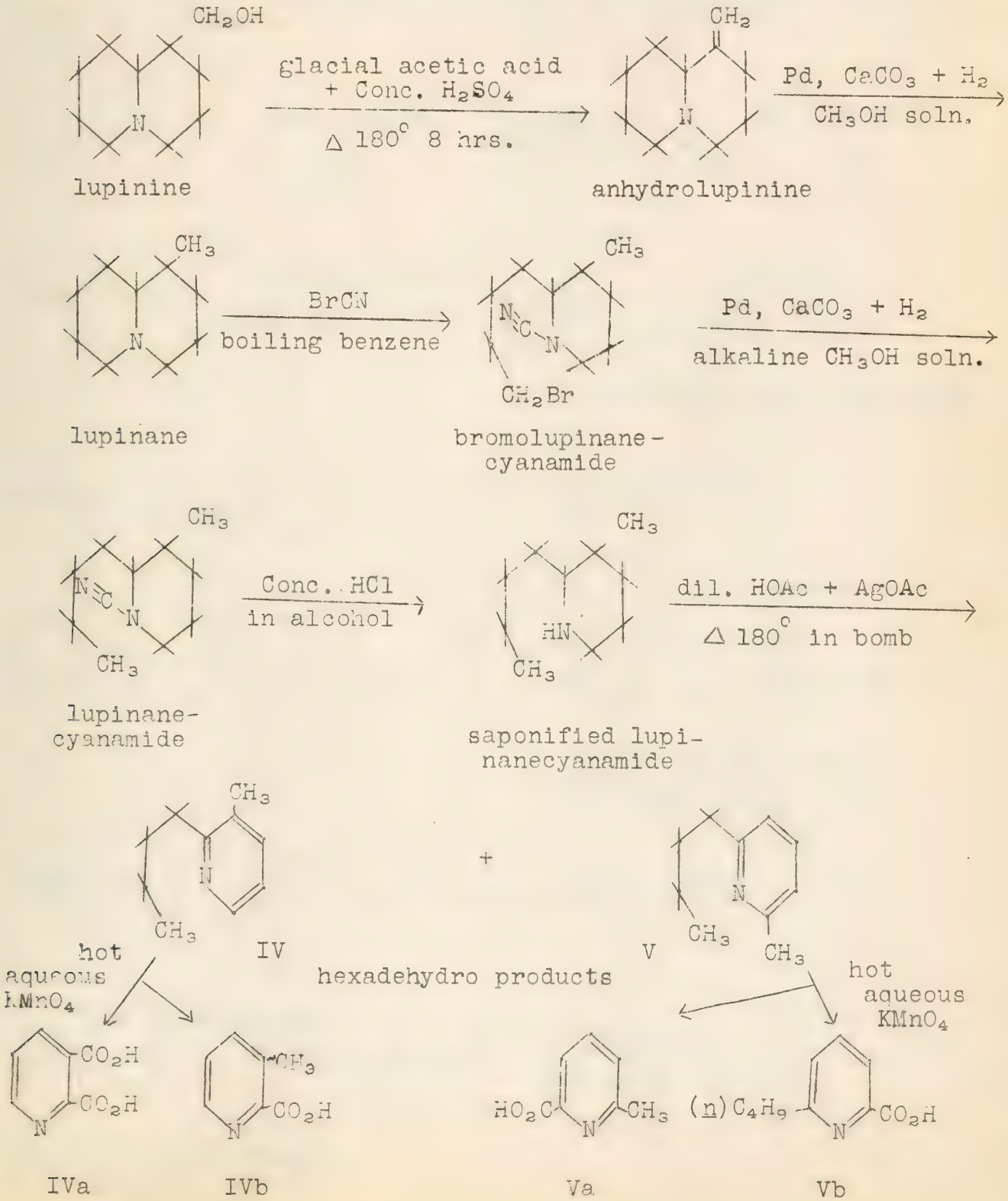
I II III

Lupinine (II) was first isolated and purified in 1881 by Baumbert. Its empirical formula, $C_{10}H_{19}ON$, was first established in 1902 by Willstäter and Fourneau. The first partial explanation of its structural formula was brought about in 1927 by Karrer and his coworkers with the use of Hofmann's exhaustive methylation. From this data two structures were possible. Since lupinane prepared from lupinine by Schöpf in 1928 and 1-methylnorlupinane synthesized by Winterfeld were identical, formula II for lupinine is correct. Lupinine was synthesized by Clemo in 1937. He obtained two racemic forms which were not resolved, m.p. 59° and 81°C. The natural lupinine has a specific rotation in ethyl alcohol $[\alpha]_D = -20.6°$ to $-21.0°$, m.p. = 68-69°C.

The parent substance, norlupinane (III), has not been found in nature. It was prepared by Willstäter and Fourneau in 1902 but its structure was not known then. They made it by the decarboxylation of lupininic acid which in turn was obtained from the oxidation of natural lupinine. In 1937 Clemo synthesized two forms of norlupinane each by a different method. One of these forms was identical with that obtained from natural lupinine. These were called cis and trans and were not interconvertable.

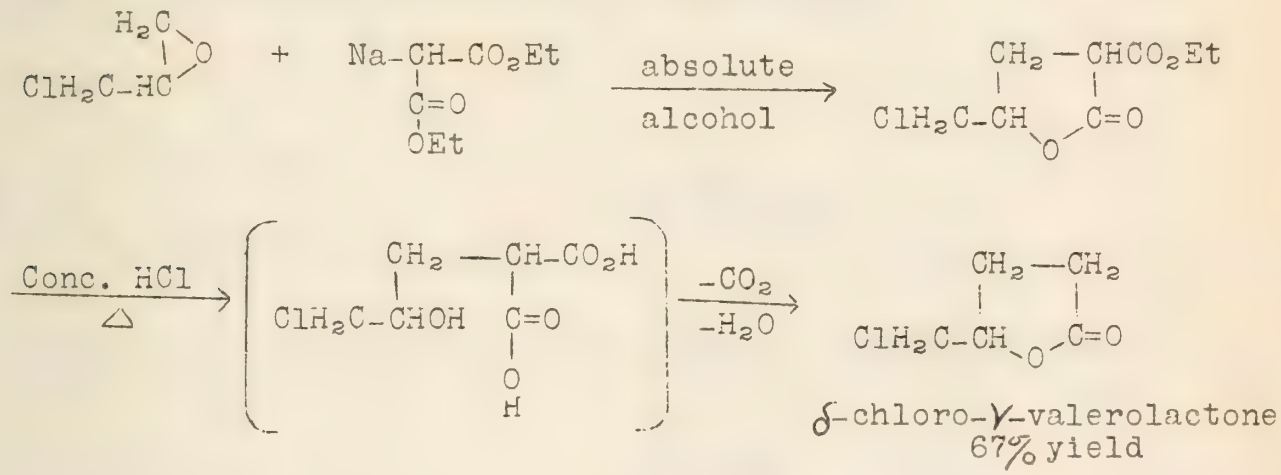
In 1931 when Winterfeld and Holschneider ran the following series of reactions on natural lupinine they obtained evidence for the existence of a structural isomer of lupinine, allolupinine (I).

However, Karrer could not find any evidence for a heterogeneous mixture in natural lupinine. He crystallized 15 g. nine times from ethyl alcohol. Each fraction had the same melting point and specific rotation. Schöpf came to the same conclusion after fractional crystallization of lupinine from acetone and quantitative preparation of the benzoate.



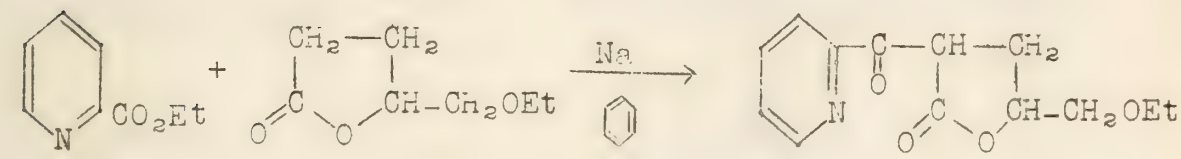
The lupinine (II) used as starting material must have contained also allolupinine (I) since compounds V, Va [α'-methylpicolinic acid] and Vb [α'-(n) butylpicolinic acid] would be derived from allolupinine (I) by the same reactions that compounds IV, IVa (quinolinic acid) and IVb (β-methylpicolinic acid) would be derived from lupinine (II).

In order to study the properties of allolupinine it was decided to synthesize it. The following reactions show the procedure used.

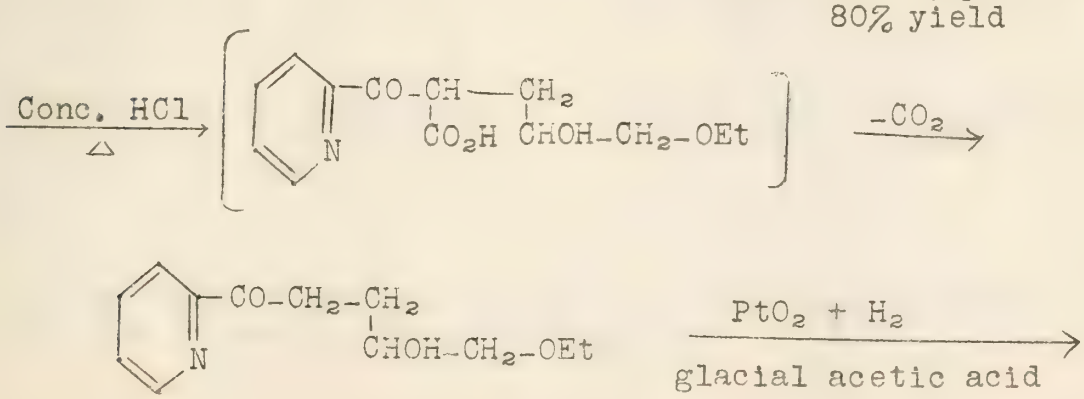


δ-chloro-γ-valerolactone
67% yield

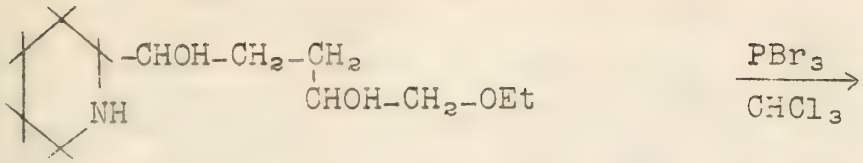
δ-ethoxy-γ-valerolactone
90% yield



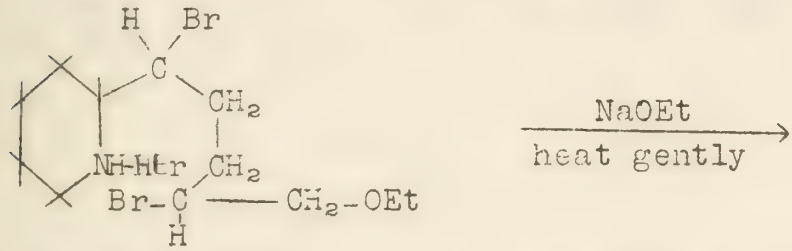
α-pyridyl-α'-[δ-ethoxy-γ-valerolactonyl] ketone
80% yield



α-pyridyl-α'-[δ-ethoxy-γ-oxy-n-butyl] ketone
94% yield

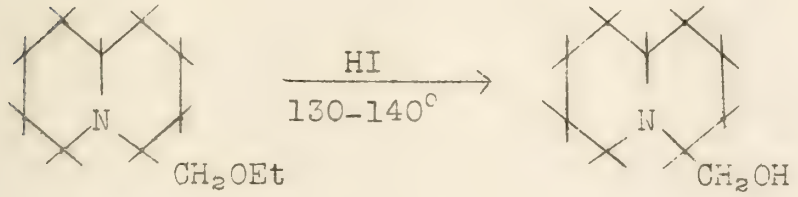


α-[α'-piperidyl] α,δ-dioxy-ε-ethoxy-n-pentane



α-[α'-pyridylhydrobromide] α,δ-dibromo-ε-ethoxy-n-pentane

1-bromo-4-ethoxymethyl-norlupinane 1,2-dehydro-4-ethoxymethyl-norlupinane



4-ethoxymethylnorlupinane allolupinine M.P. 123-125°C.

A small amount of oil was also obtained which was not analyzed. This was probably the other isomer.

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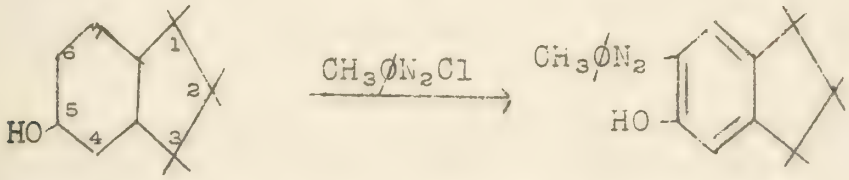
Reported by Hugh W. Stewart
April 17, 1949

THE MILLS-NIXON EFFECT

Assuming the tetrahedral character of the carbon atom and the Kekulé structure for benzene, it appears that the external valences of the carbon atoms in the benzene nucleus would not be directed as if from the center of a hexagon but would be bent slightly to the side away from the double bond.

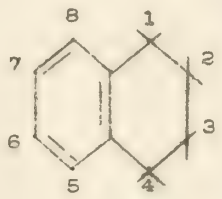
A force which would tend to push apart or bring together more closely any adjacent pair of the external valence radii should also tend to make the nuclear double bonds immobile, thus fixing the structure of the benzene ring.

Mills and Nixon found that the coupling product of diazotized p-toluidine and 5-hydroxyhydrindene was almost completely the 6-substituted derivative.



Bromination led to the 6-bromo derivative.

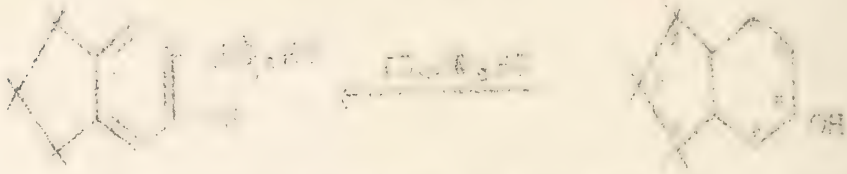
Mills and Nixon proposed that the structure of tetralin is

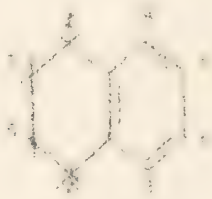


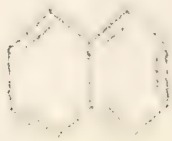
For evidence they cited reactions carried out earlier on the bromination of 6-hydroxytetralin and of 6-acetaminotetralin and also on the coupling of diazotized aniline with 6-hydroxytetralin. In each case the product was mainly the 1-substituted derivative.

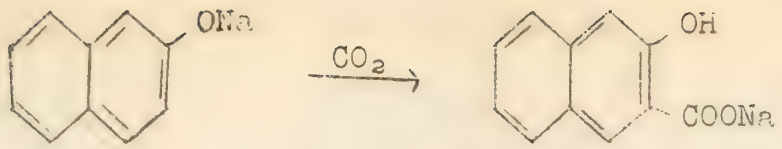
Thompson proposed that the structure for naphthalene which is the least strained is

From this it is possible to devise a mechanism by which an anionoid substituent in the β-position can direct a cationoid reagent into the 3-position, as



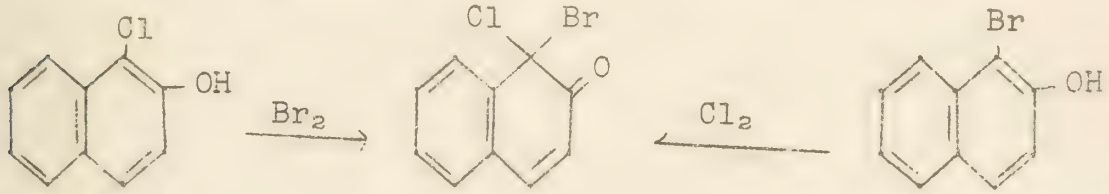




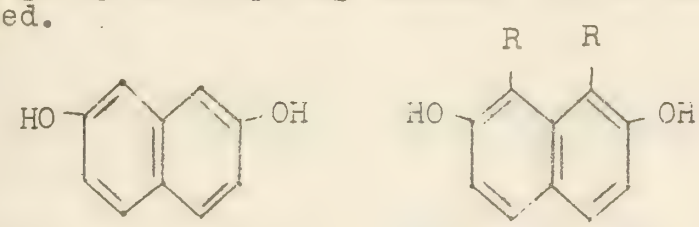


Fieser did much work relating to the Mills-Nixon effect. Etherification of β-naphthol with methanol and a mineral acid does not occur if C_1 is substituted. This is not due to steric hindrance.

1-Chloro- (or bromo-) 2-naphthol on halogenation does not form the 1,3-dihalo derivative as would be expected if the naphthol behaved like a phenol, but a keto halogenide results.

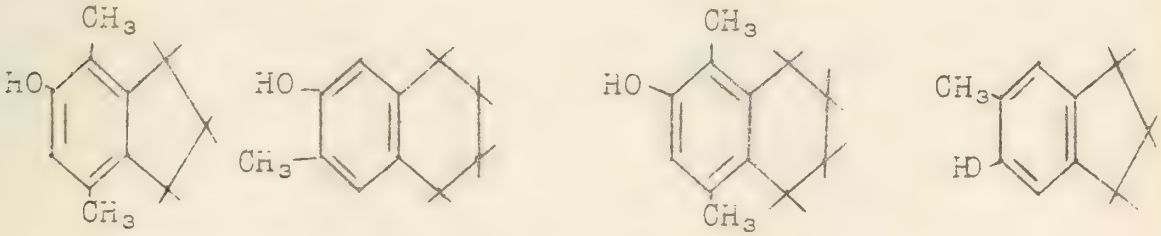


β-naphthol couples at C_1 but if this position is blocked by a stable group no coupling occurs. In no case is the C_3 position attacked.



I II

I couples at C_1 and C_8. II does not couple at all. This seems to eliminate the possibility of an unsymmetrical structure for naphthalene.



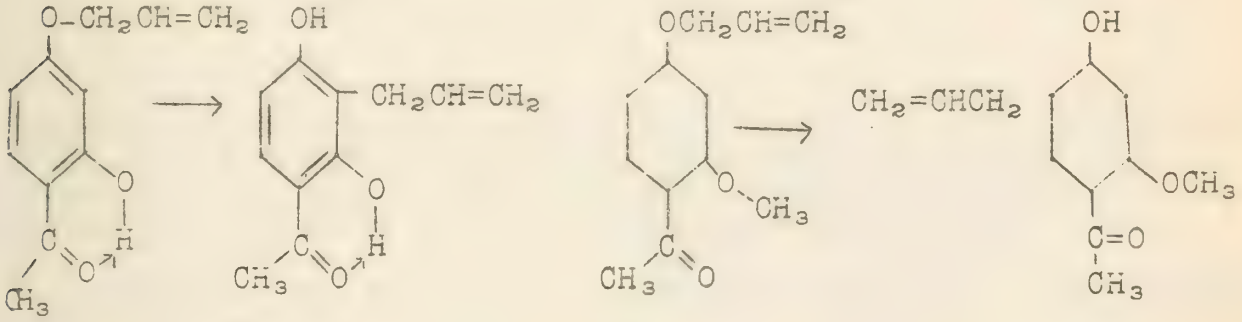
III IV V VI

III, IV and V couple readily under similar conditions. VI does not couple under these same conditions. However, it does couple in a solution which is only slightly alkaline.

From the rates of hydrolysis of nitrobromo-naphthalenes, -tetralins and -hydrindenes, McLeish and Campbell concluded that

the structures of the parent hydrocarbons are

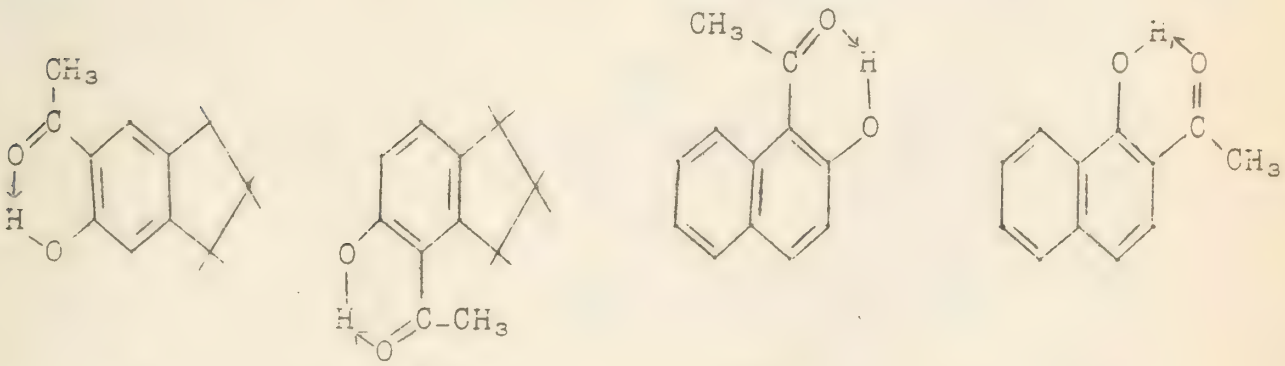
Baker and Lothian found that the rearrangement of 4-O- allylresacetophenone produced 3-allylresacetophenone, whereas 2-O-methyl-4-O-allylresacetophenone gave rise to 2-O-methyl-5-allylresacetophenone.



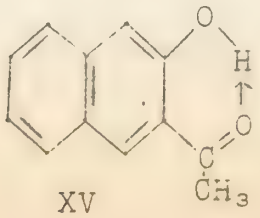
VII VIII IX X

Owing to chelation in VII the bonds should be stabilized. The analogous propiophenones and benzaldehydes underwent the same rearrangements.

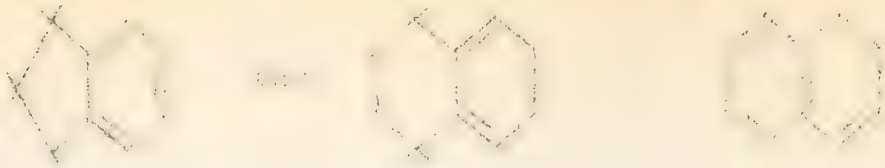
Baker and Carruthers determined that the following compounds were chelated by means of physical methods.



XI XII XIII XIV

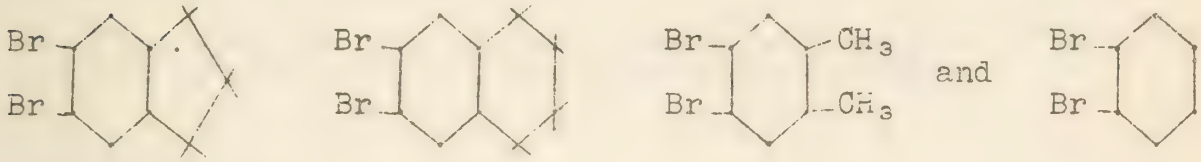


XV



XII is not chelated nearly so much as XI. XIII, XIV and XV are chelated to about the same extent. XV is the only one of the isomeric naphthalenes which is highly colored. However, it shows none of the properties of an o-quinoid. The methyl ether of XV is not colored.

From the dipole moment of the Br-C-C-Br fragment in

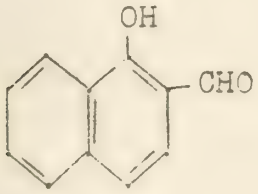


Sidgwick and Springall concluded that the bonds in hydrindene are fixed with a common C-C bond, but that there is resonance in tetralin as in benzene and o-xylene. The dipole moment data indicate the structure of these compounds in the resting state.

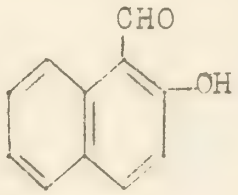
Kistiakowsky, et.al., concluded from the heat of hydrogenation that there cannot be hindering of the resonance in hydrindene.

That substitution reactions, especially those with high activation energies, cannot be used to locate double bonds is shown by the fact that nitrogen tetroxide reacts with 6-hydroxytetralin to produce the 7-nitro derivative, while bromine reacts with the hydroxytetralin to produce the 5-bromo derivative. Thus, a double bond could be located either between C_5-C_6 or between C_6-C_7 depending on the reaction chosen.

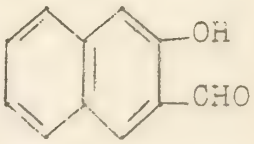
Recently Arnold has attempted to locate the double bonds in naphthalene, tetralin and hydrindene by a physical method which is more nearly free from objections than are the chemical methods heretofore used. The acidities of the following compounds were measured:



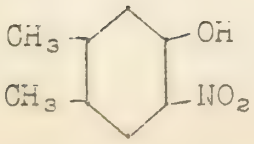
XVI



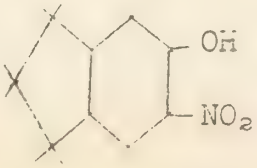
XVII



XVIII



XIX



XX

XXI

Because XVI and XVII are vinologs of formic acid, they should be more acidic than XVIII if the structures are correct. This was found to be true. XVIII was more acidic than β-naphthol, thus indicating there is some of the naphthalene with a C_2-C_3 double bond.

The acidities of XIX, XX and XXI were almost identical, indicating similar bond structure. These results were interpreted as meaning that there is no appreciable stabilization of double bonds caused by ring structure.

It seems now that the Mills-Nixon effect does not hold rigidly, but the problem is still far from being settled.

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Reported by E. Welch
April 17, 1940

THE POLYMERIZATION OF BUTADIENE

Ziegler--University of Heidelberg

In a previous paper with Dersch and Wollthan, Ziegler showed from the study of relatively low molecular weight compounds that there was no simple principle of polymerization of butadiene, but that one had to deal with random 1,2- and 1,4-addition. This work was only qualitative in nature; the quantitative relation of the two modes of addition remained to be found, as well as an answer to the question as to whether and in what manner the numerical ratio of the two types of addition depended on the conditions of reaction.

By the addition of butyl-lithium to butadiene, a mixture of reaction products of the type I below results, in which n has a definite range of values whose average depends upon the amount of butadiene used. With water these adducts yield various unsaturated hydrocarbons of the type II below; these may be hydrogenated further to form saturated paraffins III .

$$C_4H_9(C_4H_6)_n\cdot Li \qquad C_4H_9(C_4H_6)_n\cdot H \qquad C_4H_9(C_4H_8)_n\cdot H$$

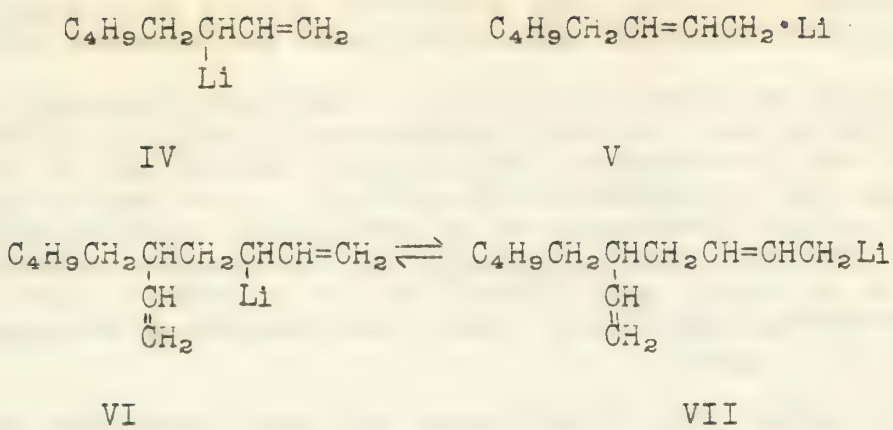
I II III

In earlier studies on the reaction of three moles of butadiene with one of butyl-lithium, after hydrogenation besides n-octane no further normal paraffins could be isolated. The mixture was oily; after distillation the higher fractions were not solid and altogether the product was quite different from a mixture of normal paraffins $(C_4H_8)_n\cdot H_2$, n = 2 to 9, which was prepared as a comparison. Since each 1,2-linkage of a butadiene molecule in the middle of a longer chain of butadiene molecules leads to the formation of a vinyl, or after hydrogenation to an ethyl sidechain, it was logical to decide on the presence of 1,2-addition in the substance resulting from the reaction of butadiene and butyl-lithium.

$$-CH_2-CH=CH-CH_2 \,\vdots\, CH_2-\underset{\underset{CH_2}{\|}}{CH} \,\vdots\, CH_2-CH=CH-CH_2-$$

1,4- 1,2- 1,4-

The isolation of the n-octane signifies nothing, since it contains only one butadiene unit and could result either by primary 1,2-addition of the butyl-lithium to give IV , or by 1,4-addition to give V below. A branching can occur only upon the addition of a second molecule of butadiene; this is apparent when one assumes an allylic shift for the first adducts and the fixation of the second butadiene with the 1,2-adduct to give VI $\rightleftharpoons$ VII .

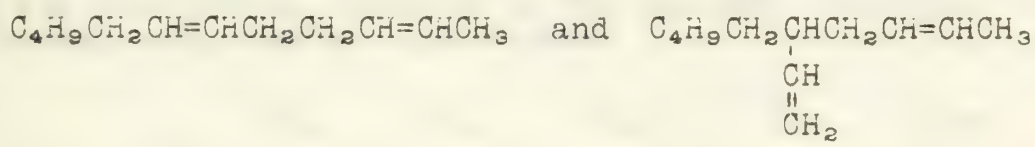


IV V

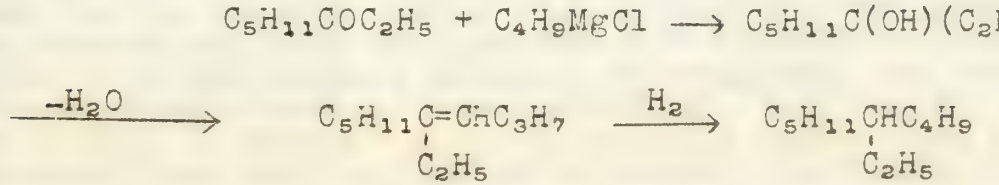
VI VII

The apparent lack of n-paraffins with more than eight carbon atoms in the mixture recovered from the butyl-lithium butadiene reaction can be explained by the assumption of an exclusive 1,2-addition. This, however, cannot be the case because analogous experiments carried out with benzyl-lithium also gave trivial amounts of n-benzyl paraffins. Therefore, the failure to isolate n-paraffins of more than eight carbon atoms in the butyl-lithium butadiene polymer arises only from the experimental difficulty of recognizing small amounts of n-paraffins in the presence of large amounts of branched chain compounds.

To test the correctness of this conclusion the "dodecane fraction" of paraffins resulting from butyl-lithium was intensively studied. This fraction consists almost entirely of two compounds, n-dodecane and 5-ethyldecane, which are formed by the hydrogenation of the two doubly unsaturated hydrocarbons,



The optimal proportions of butyl-lithium and butadiene to secure the greatest yield of dodecane fraction was found to be 1.75 mols butadiene to one mol of butyl-lithium. With these proportions and using ether as a solvent, about thirty per cent of the gross reaction products consists of dodecane fraction. By a careful, repeated vacuum distillation through a Widmer column a large amount of this fraction was separated into two distinctly different parts, of which the higher-boiling was at once recognized as n-dodecane. The lower-boiling fraction was believed to be 5-ethyldecane, which was unknown. This compound was prepared by the following synthesis:



The properties of the substance thus prepared agreed with those of the low-boiling fraction of the dodecane fraction.

Since physical constants alone do not suffice for the certain identification of liquid hydrocarbon isomers, the oxidative degradation of the doubly unsaturated precursor of the 5-ethyldecane was carried out. For this to be possible, the unhydrogenated hydrocarbons $C_{12}H_{22}$ had to be separated; during this process certain indications of cis-trans isomerism were noted. By chromic acid oxidation of the low-boiling fraction of unsaturated compounds n-amylsuccinic acid, $C_4H_9CH_2\underset{\underset{COOH}{|}}{C}HCH_2COOH$ was produced; this indicated that the unsaturated hydrocarbon was 5-vinyl-n-decene-2, from which by hydrogenation 5-ethyldecane would result.

This separation showed clearly that both 1,2- and 1,4-addition occurred in the polymerization of butadiene. So far as the authors' methods of fractionation could determine, the ratio of 5-ethyldecane to n-dodecane was three or four to one, indicating a considerable preponderance of 1,2-linkages.

The question then arose as to whether the ratio of abundance of the two kinds of addition remained the same in longer chain polymers; this was not answered positively but the authors apparently favor the opinion that it does, since the reactive end of the molecule of the growing alkyl-lithium polymer has always the same constitution regardless of the length of the chain. In connecting the known constitution of the lower fractions with the higher, they suggest that if q is the proportion of the normal hydrocarbon as shown in the dodecane fraction, then q^2 will be the per cent of normal hydrocarbon in the hexadecane fraction, and q^3 the per cent normal compound in the eicosane fraction. Thus the following table may be constructed:

	C_{12}	C_{16}	C_{20}	C_{24}	C_{28}
30°	0.25	0.0625	0.0156	0.004	0.001
100°	.80	.64	.50	.40	.32

It is at once apparent that at 30°, there must be a vanishingly small proportion of normal hydrocarbons of high molecular weight; this would account for the oily character of the low-temperature product.

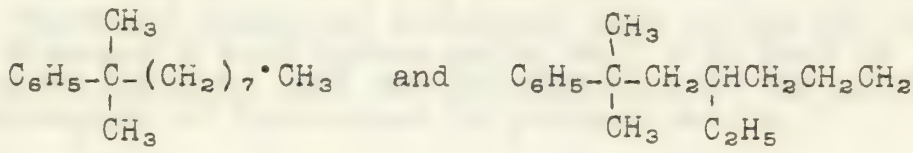
Next the influence of the experimental conditions on the ratio of 1,2- and 1,4-addition was investigated. Beginning with the assumption of an allylic rearrangement or tautomerization of the metallic end of the alkyl-lithium polymer, it was suspected that the two isomers could be in equilibrium when present in varying amounts and that they reacted with different velocities. By means of a very gradual addition of butadiene, and consequent continuous displacement of the equilibrium, then for the most part the isomer of greatest speed of reaction must react; by reversing the conditions and keeping the butadiene concentration high, then the rate of addition of the butadiene might exceed the rapidity

of the opposing rearrangement of the isomers. As a result, the product corresponding to one state of the tautomeric equilibrium could develop to the practical exclusion of the other. It would be a plausible assumption that the isomer containing more energy would react more readily.

In carrying out the experimental testing of these beliefs the solvent, temperature and speed of addition of butadiene to the butyl-lithium solution were varied.

The only condition which seemed to have any effect was that of the temperature at which the initial reaction occurred. In a test in which butadiene was added all at once to butyl-lithium the temperature rose to 60-72°, from the heat of the reaction; from this run nearly equal amounts of n-dodecane and 5-ethyldecane were obtained, while in all other runs, carried out at 25-30°, the ratio of 5-ethyldecane to n-dodecane was about 3:1. A second set of experiments was then carried out in which the temperature was varied from 100° (in an autoclave) to -50°. From the high temperature reaction about 80 per cent n-dodecane was recovered, while from the low temperature run only about 5 per cent of the dodecane fraction was normal. From the latter run it was possible to isolate quite pure 5,7-diethyl dodecane (hexadecane fraction) and 5,7,9-triethyl tetradecane (eicosane fraction).

The authors next became interested in knowing how the course of the reaction would be influenced by the use of other alkali metals as centers of reaction. For this purpose phenylisopropylpotassium was used. The two hydrocarbons corresponding to n-dodecane and 5-ethyldecane are



For comparison they may easily be prepared by coupling the potassium compound with n-octyl iodide or 2-ethyl-1-iodohexane. At 5 mm. pressure the separation of boiling points is 11° being 139° and 128°.

As was expected, the quantitative distillation analysis of the phenylisopropyloctanes obtained from butadiene gave two fractions of the correct boiling point for these two hydrocarbons. The influence of the temperature of the initial reaction was about the same as with the lithium compound. Combining the potassium and lithium experiments, we have the following table:

Temperature	-70	-50	+30	+35	+60	+80	+110
Per cent normal hydrocarbon	12*	8	20	25*	47	75*	85

The values marked with an * are by K; the others by Li.

In general the results from the two metals agree well. There is an inconsistency in the value for the lowest temperature, but this is unimportant, for since there is so very little of the one component the errors may be large.

Previous attempts of the authors to employ cleavage of the polymer with ozone had been inconclusive, since the polymers prepared at relatively low temperatures have comparatively few double bonds in the main chain and, therefore, could not be split into sufficiently small pieces. The vinyl sidechains should give formaldehyde, but even this does not appear in the proper amount. After learning how to produce a polymer with considerably more 1,4-linkages, ozonization was returned to and from a butyl-lithium polymer prepared at 150°. Sixty per cent of the theoretical amount of succinic acid was obtained. On the other hand, not a trace of succinic acid could be obtained from the ozonization of the polymer prepared at -70°. Thus the evidence from ozonization bears out the information gained in other ways.

With Dersch and Wollthan, Ziegler had observed that in hydrogenating the product from butyl-lithium butadiene with "mild" catalysts, about 10 per cent of the double bonds remained as more difficult to saturate, and the opinion was given that these were in vinyl sidechains. This is now known to be incorrect since a far greater amount of vinyl sidechains must be present; steric hindrance is now believed to be the controlling factor.

After the work described had been completed, Simonsen's work on purely thermally catalyzed butadiene came to the notice of the authors. Simonsen's work agrees quite well with that of Ziegler, which seems to indicate that the constitution of the polymer is fairly independent of the method of polymerization.

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Reported by L. B. Wakefield
April 24, 1940

ORGANIC REACTIONS INVOLVING THE ALKALI AMIDES

Alkali amides have become a much used reagent in synthetic organic chemistry because of their ability to promote condensation reactions, to introduce amino groups into a molecule and to remove the elements of water or of a hydrohalide acid. The reactions of the alkali amides in liquid ammonia and in inert solvents with the different classes of organic compounds are presented.

I Hydrocarbons

a. Saturated.--As would be expected, the saturated hydrocarbons exhibit no reaction whatsoever in liquid ammonia toward the alkali amides. At elevated temperatures, however, the higher paraffin hydrocarbons are cracked to lower hydrocarbons and hydrogen.

b. Acetylenic.--Acetylene and all true acetylenic hydrocarbons, i.e., those containing the free methine group, ≡CH, react with sodium amide in liquid ammonia to form the salts, RC≡CNa, in theoretical yield,

$$RC{\equiv}CH + NaNH_2 \longrightarrow RC{\equiv}CNa + NH_3$$

Picon and Bourguel recommend the use of sodium amide over sodium in that the reaction is more rapid and complete, and the possibility of reduction products is eliminated. By treatment of the acetylenic sodium salts with the corresponding alkyl halide, the monoalkylated acetylenes are obtained in good yields,

$$RC{\equiv}CNa + R'X \longrightarrow RC{\equiv}CR' + NaX$$

$$R = CH_3, \quad \underline{n}\text{-}C_4H_9, \text{ etc.}$$

Carothers and Jacobson have obtained 1-(methyl, ethyl, butyl or heptyl)-2-vinyl acetylene in this manner in 82 per cent yields. Use of dimethyl sulfate as the alkylating agent has been reported.

Disubstituted acetylenes of the type RC≡CR in the presence of sodium amide undergo the Favorsky rearrangement and are transformed into a "true" acetylene in accordance with the equation,

$$RC{\equiv}C(CH_2)_nCH_3 + NaNH_2 \xrightarrow[\text{paraffin oil}]{160^\circ C.} R(CH_2)_{n+1}C{\equiv}CNa + NH_3$$

The isomerization by sodium amide is due to its tendency to form an insoluble salt with the true acetylene and thus shift the equilibrium system. An interesting application of this rearrangement was employed by Bourguel for increasing the length of the carbon chain of an acetylenic hydrocarbon,

$$RC{\equiv}CH \longrightarrow RC{\equiv}CNa \longrightarrow RC{\equiv}CCH_3 \longrightarrow RCH_2C{\equiv}CNa$$

$$RCH_2C{\equiv}CNa \longrightarrow RCH_2C{\equiv}CCH_3 \longrightarrow RCH_2CH_2C{\equiv}CNa \longrightarrow \text{etc.}$$

(Yield in each step is 80 per cent)

c. Aromatic.--The salts of compounds containing a methane hydrogen activated by two or more phenyl groups have been formed by treatment of the hydrocarbon with potassium amide in liquid ammonia. The formation of the potassium salt of triphenylmethane has been reported. Fluorene and indene both yield corresponding sodium salts on treatment with sodium amide at 100-150°C.

II Halogen Compounds

a. Paraffin monohalides.--Reactions of monohalides consist (1) in the ammonolysis of the alkyl halide to an alkyl amine, and (2) in the abstraction of hydrogen halide from the alkyl halide to form an unsaturated hydrocarbon,

$$(1)\quad RCH_2CH_2X + NaNH_2 \longrightarrow RCH_2CH_2NH_2 + NaX$$

$$(2)\quad RCH_2CH_2X + NaNH_2 \longrightarrow RCH{=}CH_2 + NaX + NH_3$$

Chablay reports the formation of methyl amine on treatment of methyl iodide with sodium amide in liquid ammonia but that the higher alkyl halides react to produce unsaturated hydrocarbons in amounts increasing with the molecular weight of the alkyl group.

$$CH_3CH_2I \longrightarrow CH_2{=}CH_2 \qquad 5.4\ \%$$

$$CH_3CH_2CH_2I \longrightarrow CH_3CH{=}CH_2 \qquad 37\ \%$$

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>CHI \longrightarrow CH_3CH{=}CH_2 \qquad 69.6\ \%$$

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>CHCH_2Cl \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>C{=}CH_2 \qquad 83.6\ \%$$

b. Unsaturated monohalides.--Acetylenic hydrocarbons are obtained in good yields by treating halogen derivatives of ethylenic hydrocarbons with sodium amide in an inert liquid (toluene, vaseline, paraffin oil) at approximately 160°C.,

$$RCX{=}CH_2 + 2NaNH_2 \longrightarrow RC{\equiv}CNa + NaCl + 2NH_3$$

$$RCH{=}CHX + 2NaNH_2 \longrightarrow RC{\equiv}CNa + NaCl + 2NH_3$$

(X = halogen, generally Cl or Br; R = alkyl or hydroaromatic)

Thus Marvel and Davis prepared 3-ethyl-3-methyl pentyne in 75 per cent yield by heating $NaNH_2$ with 3-ethyl-3-methyl-2-chloropentene-1 in mineral oil at 160-175°C.

$$CH_3{-}CH_2{-}\underset{\underset{CH_3}{|}}{\overset{\overset{C_2H_5}{|}}{C}}{-}C(Cl){=}CH_2 \longrightarrow CH_3CH_2{-}\underset{\underset{CH_3}{|}}{\overset{\overset{C_2H_5}{|}}{C}}{-}C{\equiv}CH$$

If the reaction yields a disubstituted acetylene with at least one alkyl substituent, a Favorsky rearrangement may occur. Bourguel concludes that sodium amide is superior to sodium hydroxide in the abstraction of HX since polymerization and reduction are minimized and yields increased.

c. Paraffin polyhalides.--Treatment of 1,1- or 1,2-paraffin dihalides with sodium amide under an inert solvent yields the corresponding acetylenic hydrocarbons as generalized in the following equations,

$$RCHXCH_2X + 3NaNH_2 \longrightarrow RC{\equiv}CNa + 2NaBr + 3NH_3$$

$$RCX_2CH_3 + 3NaNH_2 \longrightarrow RC{\equiv}CNa + 2NaBr + 3NH_3$$

$$RCH_2CHX_2 + 3NaNH_2 \longrightarrow RC{\equiv}CNa + 2NaBr + 3NH_3$$

(Here as in the previous section the true acetylenes are the chief products.)

d. Aromatic halides.--Chloro-, bromo-, and iodobenzenes (fluorobenzene is inert) react very rapidly with a liquid ammonia solution of potassium amide at -33°C. to give aniline and diphenylamine, with smaller quantities of triphenylamine and p-aminobiphenyl in proportions which depend upon the experimental conditions. Competition reactions indicate the following order of ease of replacement of halogens in unsubstituted phenyl halides,

$$Br > I > Cl >>> F$$

N-Mono- and disubstituted aniline derivatives have been obtained by treatment of the aryl halide in ether solution with the corresponding mono-, or dialkyl substituted lithium amide.

$$C_6H_5Cl + LiN(Et)_2 \longrightarrow C_6H_5N(Et)_2 + LiCl \qquad (60\text{-}90\%)$$

III Alcohols and Phenols

Aliphatic alcohols and phenols are converted to the salts by an alkali amide in liquid ammonia.

$$ROH + NaNH_2 \longrightarrow RONa + NH_3$$

The sodium salts of the naphthols are best prepared in liquid ammonia solution by action of sodium amide on naphthol since reduction products are formed when Na alone is used.

Mlle. Gredy has used $NaNH_2$ in preparing the methyl ethers of a number of acetylenic alcohols according to the equation,

$$RC{\equiv}CCH_2OH \xrightarrow[\text{abs. ether}]{NaNH_2} RC{\equiv}CCH_2ONa \xrightarrow{(CH_3)_2SO_4} RC{\equiv}CCH_2OCH_3$$

(80%)

IV Aromatic Amines

Aniline reacts with both potassium and sodium amides, either in the presence or absence of liquid ammonia to form a corresponding monopotassium or monosodium salt. Monopotassium anilide and derivatives can be alkylated in liquid ammonia by treatment with alkyl halides. Thus, the potassium salt of diphenyl amine is converted to the N-ethyl derivative in accordance with the equation,

$$(C_6H_5)_2NK + C_2H_5Br \longrightarrow (C_6H_5)_2NCH_2CH_3 + KBr$$

V Ketones

a. Aliphatic ketones.--The methylation and ethylation of aliphatic and mixed aliphatic-aromatic ketones by means of sodium amide has now come into general use.

$$(CH_3)_3CCOCH_3 + NaNH_2 \xrightarrow{\text{ether}} (CH_3)_3CC(=CH_2)ONa + NH_3$$

$$(CH_3)_3CC(=CH_2)ONa + EtBr \xrightarrow{\text{ether}} (CH_3)_3CCOCH_2CH_2CH_3 + NaBr$$

Nasarov has studied "n-propylation" of pinacolone, pentamethyl acetone, etc., with the conclusion that propylation is definitely more difficult than methylation or ethylation, and is best effected by the reaction of n-propyl iodide, sodium amide and the ketone in boiling benzene.

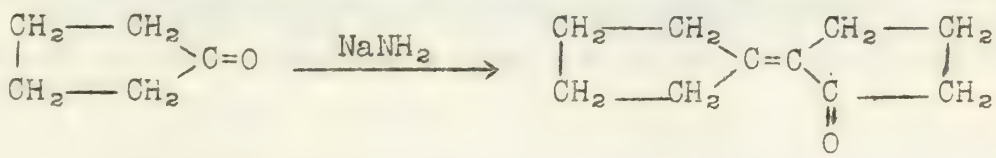
b. Mixed aliphatic-aromatic ketones.--Ketones of the type $C_6H_5COCH_2R$, $C_6H_5COCHRR'$, and $C_6H_5COCRR'R''$ have been prepared where R, R', and R" are usually methyl, ethyl, propyl, allyl or benzyl.

$$C_6H_5C(ONa)=CH_2 + EtI \longrightarrow C_6H_5COCH_2CH_2CH_3 + NaI$$

Aromatic groups, such as phenyl, as well as aliphatic groups higher than propyl, cannot be introduced into acetophenone in this manner.

In addition to alkylation by means of methyl and ethyl halides, similar reactions have been successfully studied with (1) ethylene and trimethylene halides, (2) epihalohydrins, (3) monochloroacetic esters, (4) α-iodoacetic, and β-iodopropionic esters, (5) chlorocarbonic esters, and (6) acid chlorides.

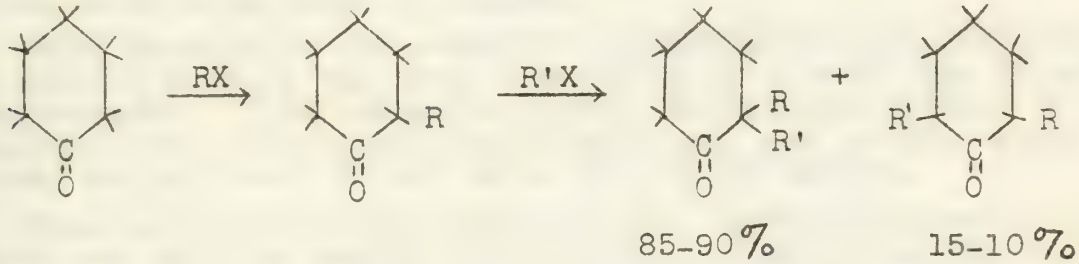
c. Cyclic ketones.--Cyclopentanone undergoes an aldol condensation in the presence of sodium amide as follows,

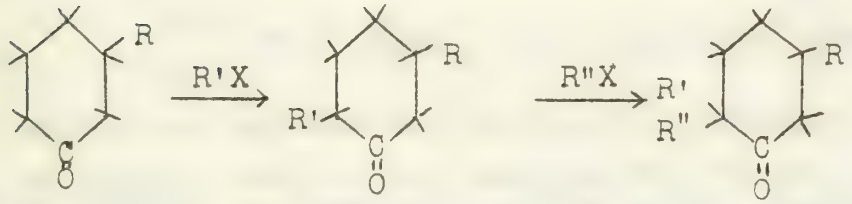


Cyclopentanone, as well as β-methyl cyclopentanone, cannot be alkylated in a satisfactory method, but α-methyl and α,β'-dimethyl derivatives may be alkylated in the usual manner, yielding, as the case may be α,α,α',α'-tetrasubstituted or α,α,α',α',β'-pentasubsti-

tuted derivatives.

As in the case of cyclopentanone, cyclohexanone is converted to cyclohexylidenecyclohexanone by an aldol condensation. Cornubert, however, by careful control of experimental conditions and working in more dilute ethereal solutions has successfully carried out alkylation according to the following scheme,

1. 

2. 

d. Preparation of acetylenic carbinols.--Treatment of ketones with acetylene in the presence of sodium or sodium amide yields the acetylenic carbinols in good yields,

$$RCOR \xrightarrow[C_2H_2]{NaNH_2} RC(OH)(R)C{\equiv}CH$$

From methylethyl ketone and vinylacetylene, Carothers obtained the corresponding vinylacetylenic carbinol in 71% yield. In the presence of strong formic acid the carbinols are isomerized to unsaturated aldehydes,

$$R_2C(OH)C{\equiv}CH \longrightarrow R_2C{=}CH{-}CHO$$

e. Scission of ketones by means of sodium amide.--Diaryl ketones of the benzophenone type are cleaved by $NaNH_2$ in boiling benzene, toluene or xylene, yielding a mixture of two products according to the equation,

$$3,4\text{-}(CH_3)_2C_6H_3COC_6H_5 \xrightarrow{NaNH_2} \begin{cases} \rightarrow 3,4\text{-}(CH_3)_2C_6H_3CONH_2 + C_6H_6 \\ \rightarrow C_6H_5CONH_2 + \underline{o}\text{-}(CH_3)_2C_6H_4 \end{cases}$$

This type of reaction appears to be general for all aromatic ketones as well as many of the mixed aliphatic-aromatic ketones.

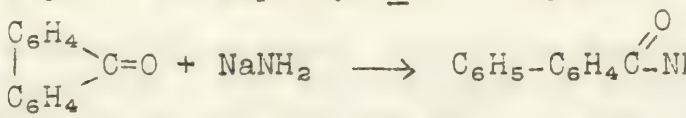
Haller, Bauer and others have observed that trialkylacetophenones are decomposed by sodium amide in accordance with the general equation,

$$C_6H_5COCRR'R'' + NaNH_2 \rightarrow C_6H_6 + RR'R''CONHNa$$

Occasionally, however, the presence of such groups as benzyl, benzohydryl, etc., promote partial scission in a reverse sense, yielding a branched chain hydrocarbon and benzamide. The heavier the groups, R and R', the greater the tendency for benzamide formation. ω,ω,ω-tribenzylacetophenone has yielded tribenzylmethane by refluxing with $NaNH_2$ in xylene.

With ketones of the structure R"R'RCORR'R" and R"R'RCOR$_3$, the reaction of $NaNH_2$ is far from general as it is with the trialkylacetophenones. With unsymmetrically substituted ketones the scission proceeds in both possible directions, but certain symmetrical ketones do not react at all with the alkali amides.

Ketones in which the carbon of the carbonyl is part of a ring system are split by $NaNH_2$. Fluorenone is thus converted in almost quantitative yield to diphenyl-o-carboxylic acid amide,



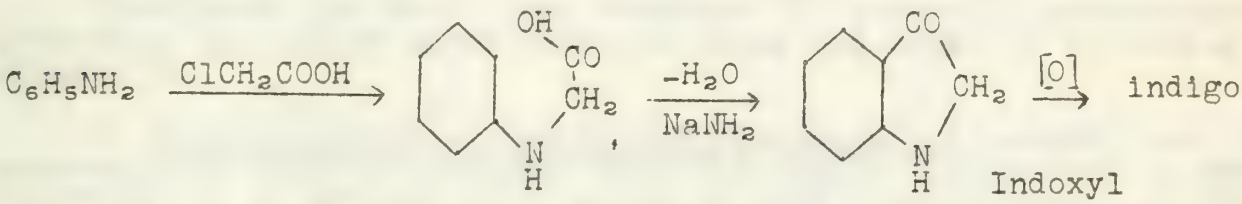
VI. Acids and Derivatives (Exclusive of Esters)

a. Acids.--Fulton has observed the formation of methane when sodium acetate is fused with sodium amide, resembling the well-known preparation of the gas from sodium acetate and soda lime.

b. Acid amides.--When considered as the mixed aquoammono carboxylic acids, it is to be expected that the amides would form metallic salts with the alkali amides in liquid ammonia.

$$RCONH_2 + KNH_2 \longrightarrow RCONHK + NH_3$$

c. Indigo synthesis.--Sodium amide has long been used as a dehydrating agent in the conversion of phenylglycine to indoxyl, an intermediate in the commercial synthesis of indigo,



d. Nitriles and related compounds.--(1) Formation of amidines: By the addition of nitrile to a solution of KNH_2 in liquid NH_3, salts of the amidines are readily prepared,

$$RC{\equiv}N + KNH_2 \longrightarrow RC(=NH)-NHNa$$

Benzamidine was obtained from benzonitrile in 15-20 per cent yield, p-toluamidine from p-tolunitrile in 60 per cent yield, and β-naphthamidine from β-naphthonitrile in 40-50 per cent yield.

Ziegler has succeeded in obtaining alkylated amidines by treatment of the Na Salts with alkyl halides.

(2) Alkylation of nitriles: Secondary aliphatic nitriles react with lithium diethylamide and similar metallic alcoholates of the

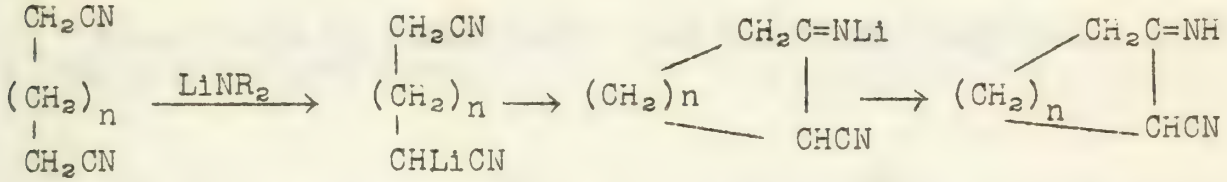
in the following equation,

$$R_2CHCN + LiNR_2 \longrightarrow R_2C(Li)CN + R_2NH$$
$$R_2C(Li)CN + R'X \longrightarrow LiX + R_2C(CN)R'$$

Attempts to extend this reaction to primary nitriles led to formation of large amounts of the Li derivative of the dimeric nitrile, particularly if the ratio of nitrile to $LiNR_2$ were 2 to 1.

$$RCH_2CN + RCH(Li)CN \longrightarrow RCH_2\overset{\overset{NLi}{\|}}{C}-CH(CN)R$$

(3) Dinitriles and large ring syntheses: Thorpe in 1909 treated adiponitrile with sodium ethoxide and obtained an iminocyclopentane. Synthesis of larger rings by this process always gave unsatisfactory yields until Ziegler proposed the use of dialkyl lithium amides as the condensing agents.



Despite their advantages, their use involves several experimental difficulties: (1) the tendency of a dinitrile to polymerize, (2) the formation of a dilithium salt of the nitrile must be prevented since only the monolithium salt undergoes cyclization.

VII Esters

a. Esters not undergoing the Claisen condensation.--Sodium amide, a base of the ammonia system, should saponify an ester in either of two ways,

$$RC(=O)-OR' + NaNH_2 \longrightarrow RC(=O)-NHNa + R'OH \qquad \text{I}$$

$$RC(=O)-OR + NaNH_2 \longrightarrow RC(=O)-ONa + R'NH_2 \qquad \text{II}$$

Experiment has shown that reaction I generally predominates, providing the sodium amide does not cause the ester to undergo condensation.

b. Esters undergoing the Claisen condensation.--$NaNH_2$ can generally be used to advantage over the alkali alcoholates in the condensation of ketones with esters to form 1,3-diketones, in that the reactions run more smoothly and rapidly and give better yields of product. In the preparation of acetylacetone from ethyl acetate and acetone, Claisen obtained a 50 per cent yield with $NaNH_2$ and a 37 per cent yield with Na as the catalyst. Benzoylacetone was obtained in 77 per cent while only 64 per cent was obtained using sodium ethoxide as the catalyst.

VIII Heterocyclic Nitrogen Ring Systems

a. Five-membered.--Due to the acidic character of the N-hydrogen atoms of pyrrole, indole, and carbazole, they may be converted to their respective sodium salts by treatment with $NaNH_2$ in liquid ammonia.

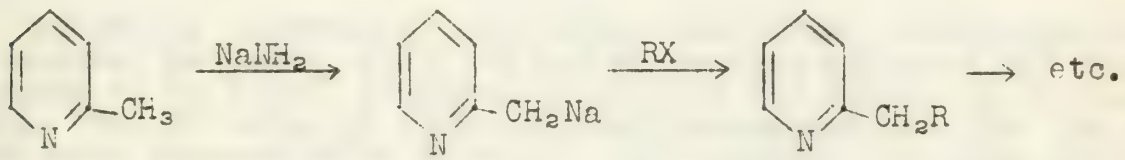
b. Six-membered.--2-Amino pyridine has been prepared in yields as high as 70-80 per cent by the action of sodium amide upon pyridine in boiling xylene, toluene or benzene.

$$C_5H_5N + NaNH_2 \longrightarrow H_2 + C_5H_4NNHNa$$

By increasing the proportion of $NaNH_2$, 2,6-diaminopyridine is obtained in approximately 50 per cent yields.

The mechanism suggested for these aminations is modelled after that of Ziegler and Zeiser who advanced the idea that $NaNH_2$ first adds to the -CH=N- bond with a subsequent loss of NaH. 2-Aminopyridines are readily alkylated to the 2-N-alkylated aminopyridines.

Recent work by Chichibabin has led to the alkylation of the 2- and 4-alkyl pyridines.



The yield of alkylated products, if alkyl chlorides are used, is not inferior to 40 per cent, and is usually 50-60 per cent of the monosubstitution product, or 70-80 per cent if disubstitution products are included. 4-Propylquinoline was obtained in 90 per cent yields and monobenzylquinaldine in 65 per cent yield.

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Reported by R. C. Gunther
April 24, 1940

PANTOTHENIC ACID

Roger Williams et al. -- Oregon State College and University of Texas
Stiller, Keresztesy and Finkelstein -- Merck Research Laboratories

In 1933 Williams and coworkers recognized the existence of a single acid substance, obtained from material of very diverse biological origin, which was capable of stimulating the growth of "Gebrüde Mayer" yeast. Because this substance is so widespread in nature it was called pantothenic acid, derived from the Greek meaning "from everywhere."

The origin of pantothenic acid in nature is rather obscure except that it is produced in soil by Aspergillus niger. Williams recognized it from the outset as a water-soluble vitamin of the B_2 complex.

Alcoholic extracts of rice bran, beef liver, crab eggs, oysters, earthworms, bacteria, milk, and egg white were prepared and electrolyzed in an 8-cell electrolysis system for thirty to forty-eight hours. The pH value of each cell was determined and then the contents were evaporated to dryness. The residues were then tested for their effect on yeast growth using 0.25 mg, 0.5 mg. and 1 mg. The growth was proportional to the amount added only in those cells of pH 3.5 to 4.8. Williams assumed, at first, the active substance became concentrated at a definite pH due to its arrival at the isoelectric point. To check this the solution was made acid so that the isoelectric point would be reached more rapidly. There was, however, no tendency to migrate even from the most acidic cells. He repeated the above using the methyl ester and observed the same result, hence he concluded the substance was not amphoteric. The behavior on electrolysis led Williams to believe he had in hand a polyhydroxy acid. Attempts to concentrate the active substance by distillation failed and since the compound was very soluble in water hydroxy groups in the molecule were assumed.

The concentration and purification of pantothenic acid was a difficult problem because:

1. Most potent source contains only 40 parts per million.
2. All salts and simple derivatives are highly soluble in water.
3. It is very difficult to crystallize.
4. It has no color or reducing property by which its isolation can be followed.
5. The esters could not be distilled.

The crucial problem was first to devise some method whereby the acid could be separated from a variety of sugars and other neutral or basic water-soluble material. The solution of the problem consisted in absorbing the acid on norite, then eluting with ammonium hydroxide, making the brucine salt and from this the calcium salt and purifying the calcium salt by the following:

1. Precipitation of the active principle from concentrated aqueous solution by absolute alcohol.
2. Treatment with $HgCl_2$ in water and alcohol solution to remove presumably basic impurities still present.
3. A thrice repeated fractional precipitation of the calcium salt from an aqueous alcohol solution with isopropyl ether and finally,
4. A fractional precipitation from pyridine with acetone.

This fraction gave a clear varnish which possessed a potency of 11,000 units. (A unit of pantothenic acid is an amount equivalent to 1 g. of the dry rice bran extract) 0.0005 γ of this material (potency 11,000 units) will stimulate yeast growth.

Analysis and Determination of Constituent Groups.--It was noted that the higher the potency of the extracts the more highly oxygenated they were. Expressed in terms of mg. of oxygen required by one mg. of the calcium salt the oxidation equivalent values of material of potencies 5,000 to 10,000 have lain between 1.05 and 1.18. On the basis of three analyses, two for nitrogen, one for calcium, the molecular weight of the free acid is calculated to be 195, 201, and 209. These values require five atoms of oxygen in the compound and the only formulas deducible are $C_8H_{15}O_5N$ and $C_8H_{12}O_5N$ with the former agreeing better with the oxygen equivalent data.

Elementary Analysis.--

	C	H	N	Ca
Calcd. for $(C_8H_{15}O_5N)_2Ca$	42.8	6.25	6.25	8.92
Found	42.06	6.30	6.54	8.77
	42.77	6.32	6.35	

This is a reasonable check considering the purity of the sample. This compound has an oxidation equivalent of 1.21 and observed molecular weights from diffusion experiments correspond well.

Ionization Constant.--Because this compound had an I.K. of 3.9×10^{-5} it was thought it could not be an α-hydroxy acid. All known α-hydroxy acids have I.K.'s of 10^{-4} or higher.

Amino and Imino Groups.--Van Slyke determinations showed the absence of significant amounts of amino nitrogen. Absence of imino and amino groups was likewise indicated by the fact that the active principle was not destroyed by treatment with para-bromobenzenesulfonyl chloride and by the lack of marked basic properties of the acid. Treatment with excess methyl iodide and subsequent hydrolysis gave an activity of 96-98 per cent which indicated the absence of tertiary nitrogen.

Amide Group.--Heating an alkaline solution of the acid failed to yield ammonia. Hence, it is not a simple amide.

That pantothenic acid possesses very feeble basic properties was shown in electrolytic experiments in which pantothenic acid, aspartic acid, and glucose were placed in the anode compartment

of a five-cell fractional electrical transport apparatus. The weakly basic aspartic acid moved into the next cell (toward the cathode) 10.8 per cent. Pantothenic acid moved 11.8 per cent. This was not merely diffusion since less than 2 per cent of the glucose had left the anode compartment.

The possibility of a substituted amide is very likely since this group would give slightly basic properties. Alkali and acid both destroy the active principle and this is in accordance with a substituted amide.

Methoxy and Methyl Imino Groups.--Muro Zeisel determinations indicated the absence of both these groups.

Olefin Unsaturation.--Catalytic hydrogenation experiments at 20° and 80° on concentrated preparations showed no loss of activity. The acid would not absorb bromine on standing, therefore, no olefinic group.

Aldehyde and Ketone Groups.--Hydrogenation with Adams' calalyst using ferric chloride as an activator failed to destroy the active principle.

Oxidation experiments using $KMnO_4$, H_2O_2 and $Ag(NH_3)_2NO_3$ indicated pantothenic acid is relatively difficult to oxidize.

Treatment with phenylhydrazine at 85° resulted in only slight loss in activity.

All evidence points to the absence of either aldehyde or ketone groups.

Aromatic Nucleus.--Koch of the University of Chicago studied the ultraviolet absorption spectrum of the active principle and found no evidence of aromatic character.

Analysis also indicates the active principle is not aromatic.

Hydroxyl Group.--The nonvolatility of both acid and ester indicated the presence of groups of this nature.

The hydrophilic nature of both acid and ester suggest the presence of hydroxyl groups.

Treating the active principle with acetic anhydride, acetyl chloride, thionyl chloride, and phosphorous pentachloride resulted in almost total loss of activity.

Experiments with hydroiodic acid indicate the presence of two hydroxyl groups.

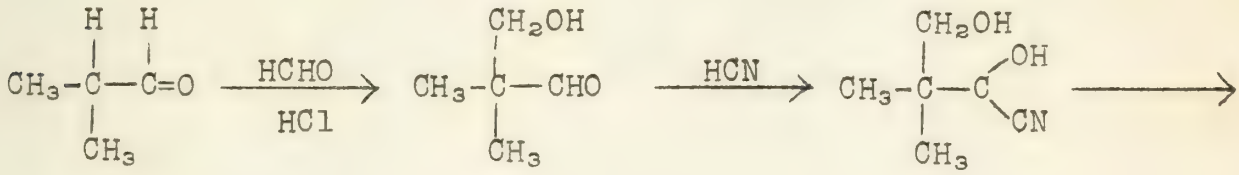
Condensation products similar to acetone-glucose are formed with acetaldehyde, benzaldehyde, and acetone.

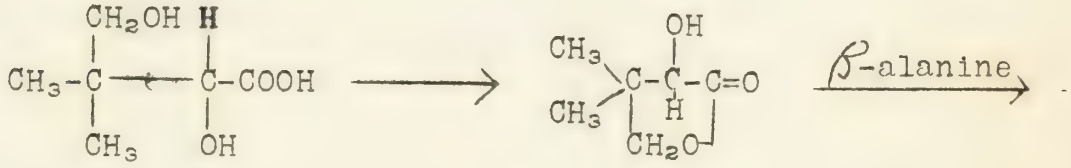
This evidence indicates the existence of two hydroxyl groups.

Cleavage Product.--β-Alanine is itself a yeast growth stimulant. This led Williams and Weinstock to believe there was a structural relationship between β-alanine and pantothenic acid. "Gebrüde Mayer" yeast growing in a little pantothenic acid does not produce more and hence becomes deficient in this essential material. When, however, the yeast was grown in a medium containing β-alanine pantothenic acid was formed and the yeast was normal.

Cleavage by hydrogen or hydroxyl ion in previous investigation indicated a peptide linkage. A highly important observation is that the physiological activity is not completely destroyed by either treatment. Because of the parallel between the residual activity and that of β-alanine it was thought that β-alanine itself was produced by cleavage of the peptide linkage. It was observed that when pantothenic acid was destroyed by acid or base the acid and base produced were in equivalent amounts. Formal titration indicated an amino group and nitrous acid destroyed 77 per cent of the residual activity. The residual activity is destroyed by esterification indicating a carboxyl group. The active cleavage product was easily shown to be β-alanine since this substance has a specific effect on yeast growth not possessed by other α-, β-, or γ-amino acids.

Soon after the isolation of β-alanine as a cleavage product Williams undertook a cooperative agreement with the Merck Research Laboratories where the crystalline lactone (cleavage product) was isolated and degraded. Its structure was shown to be α-hydroxy-β,β-dimethyl-γ-butyrolactone (I). This has been synthesized and condensed with β-alanine to produce physiologically active pantothenic acid (II). This work is unpublished.





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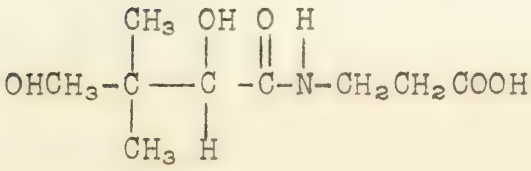

II

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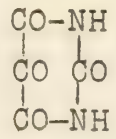
Reported by W. J. Gross
May 1, 1940.

Rudy -- Erlangen

Recently alloxan has received much attention since two of its derivatives, alloxantin and riboflavin, have worked physiological actions. Its structure shows it to be a cyclic ureide of mesoxalic acid.

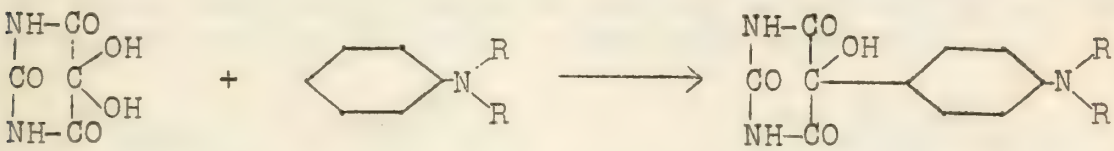


alloxan

One of its derivatives, alloxantin, is a molecular compound of alloxan and its reduced form, dialuric acid. It bears the same relation to alloxan as quinhydrone to quinone. It is used in the treatment of the osteomyelitis in gangrenous diseases which formerly could only be alleviated by the rather unpleasant blow-fly maggot therapy.

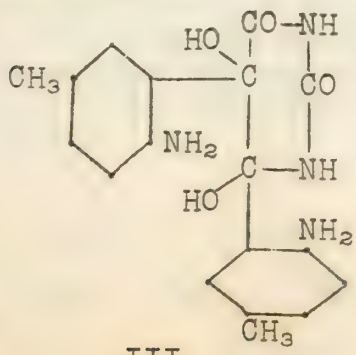
Alloxan has been prepared in numerous ways such as the decomposition of uric acid with chlorine or the condensation of mesoxalic ester and urea. A recent and more practical method consists in the condensation of malonic ester with urea to give barbituric acid followed by condensation with benzaldehyde to benzalbarbituric acid and subsequent oxidation by chromic oxide to alloxan monohydrate.

The reaction of alloxan with monoaromatic amines leads to an aryl or substituted aryl dialuric acid (II).



alloxan monohydrate R = H or alkyl II

When an alkyl group occupies the p-position the reaction occurs in the o-position. Also two molecules of the amine may add if it is present in excess. Thus, compound III is formed with excess p-toluidine.



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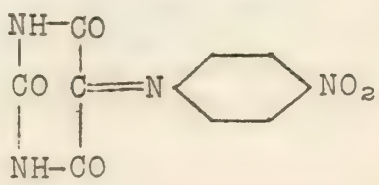
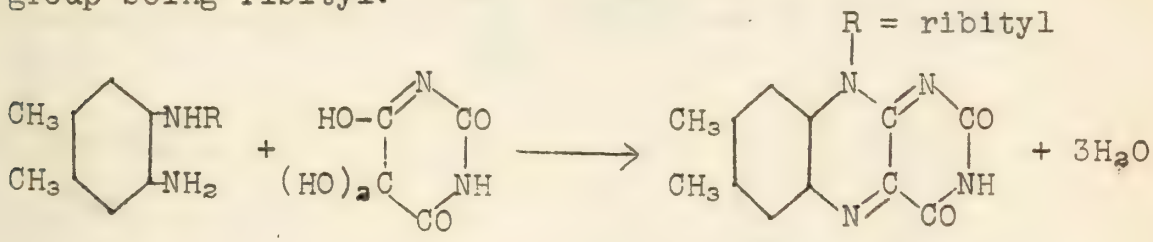


IV

A reactive amino group such as that in p-nitroaniline reacts with alloxan to give an anil (IV).

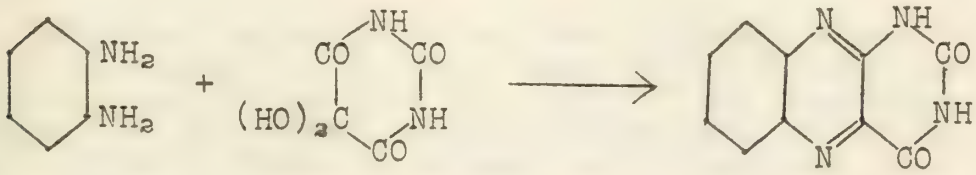
Alloxan reacts with hydrazine and phenylhydrazine to produce hydrazones providing the solution is first saturated with sulfur dioxide. In the absence of sulfur dioxide the alloxan oxidizes the hydrazine to nitrogen and is reduced to dialuric acid.

The group of compounds known as flavins has been prepared by use of diamino benzene as starting materials. Condensation of an N-monosubstituted-o-diamine with alloxan in slightly acid or neutral solution yields a fluorescent flavin dye. The reaction occurred easily with methyl or ethyl as N-substituents but when an oxy-alkyl group such as ribityl or arabinyl was placed on the amino nitrogen the reaction gave no appreciable yield of the flavin except when boric acid was used. In this reaction it is the mono-enol form of alloxan monohydrate which reacts. Kuhn and Karrer used this reaction in 1935 for the synthesis of riboflavin; the R group being ribityl.

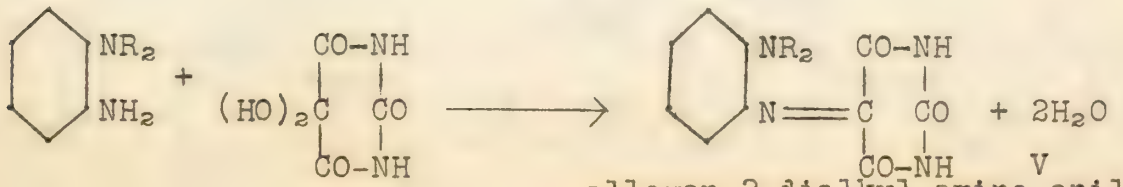


I

These flavins contain the isoalloxazine ring system. If the amine used in the above synthesis is simply o-phenylene diamine, then an alloxazine is formed. The conditions for the condensations to three fused ring compounds consist mainly in the use of a mineral acid or glacial acetic along with boric acid.



When the diamines have one amino group completely substituted or the diamines themselves are allowed to undergo the condensation with alloxan under mild conditions such as the use of dilute mineral acid or in a neutral medium, then alloxan-anils result. When the reaction was first noticed, it was thought to yield an oxy-quinoxaline carbonic acid ureide but it is now known to give the simple anil splitting out two mols of water from alloxan mono-hydrate.



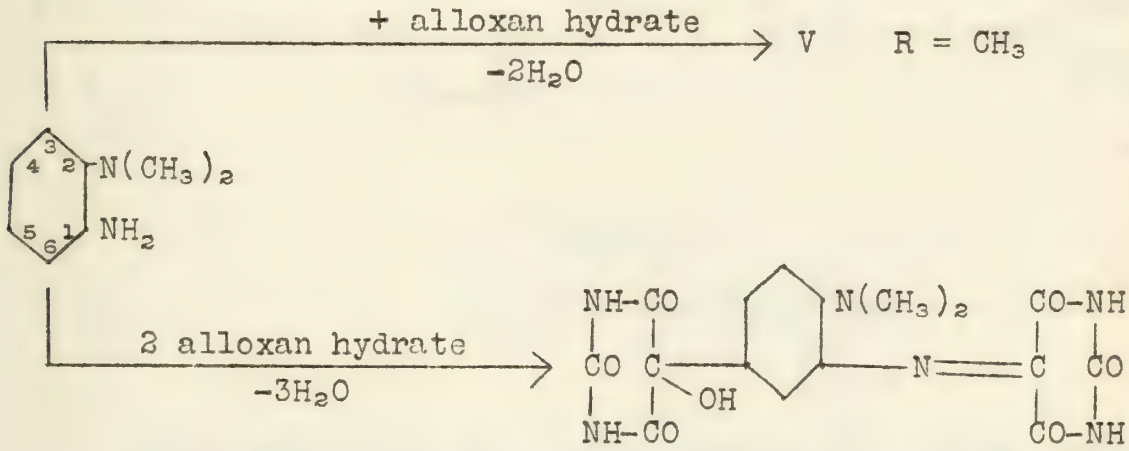
V

alloxan-2-dialkyl amino anil-5

Under the same conditions, namely, dilute acid or neutral solution, o-phenylene diamine, 5,6-diamine quinoline and 2,3-diamino pyridine give corresponding anils. The pyridine compound mentioned when condensed with alloxan in the presence of boric acid yields the tricyclic azaflavin.

Also p-phenylene diamine reacts to give the p-anil but the properties are much different even to the stability of the anil bond. In this case, it is easily broken by acids. This is in agreement with the properties of most other Schiff's bases or azomethines.

In the case of the N,N-dimethyl-o-phenylene diamine discussed above, the benzene nucleus becomes so reactive that a second molecule of alloxan reacts forming the anil dialuric acid. This further condensation is favored by excess alloxan in the presence of hydrochloric acid.

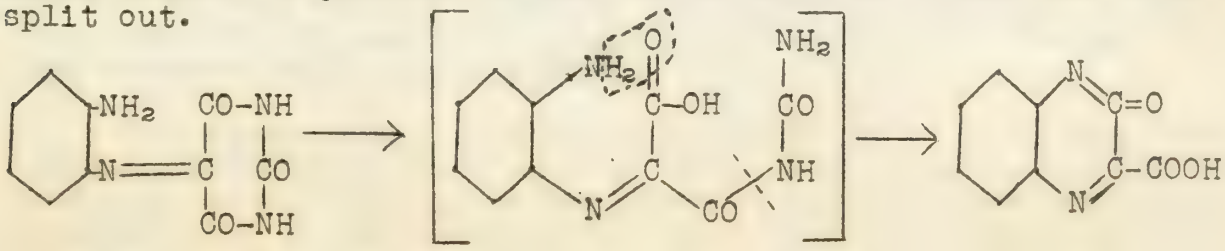


VI

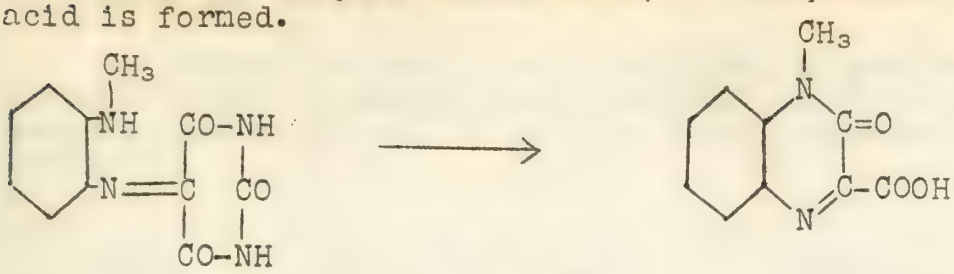
The reaction still occurs when a methyl group is placed in the 4 or 5-position, the position para to the alloxan imid rest being slightly less active than that para to the dimethylamino group. However, if two methyl groups are placed in the 4 and 5-positions, then only anil formation occurs and no reaction takes place with either o-position.

The anils of type V are amphoteric and their stability towards acids is their most outstanding property. Even when a transformation does occur on long contact with acid, the alloxan rest still clings to the original nitrogen atom and no hydrolysis occurs.

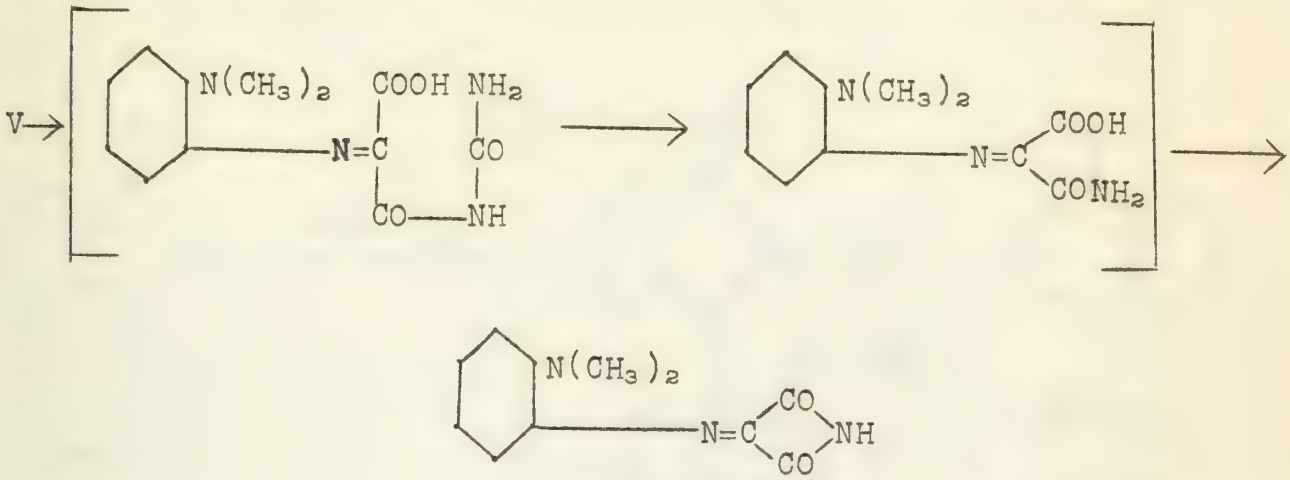
With a base such as sodium carbonate and an anil with no N-substituents, a quinoxaline carboxylic acid is formed and urea is split out.



With one alkyl N-substituent, an oxoquinoxaline carboxylic acid is formed.



With the dimethyl amino anil degradation with NaOH proceeds in a different manner since no quinoxaline can form. Also urea is not split out. However, ammonia and carbon dioxide are evolved.



The evidence for this imino malonic acid imide consists in its solubility in alkali, the reaction with CH_2N_2 to form a product more soluble in nonpolar solvents and a color reaction with H_2O_2 in hydrochloric acid solution. This reaction gives a violet color specific for a dimethyl amino group with a free <u>para</u>-position and an <u>ortho</u> >C=N- group.

The anil (V) is a strong reducing substance reducing silver nitrate at ordinary temperature.

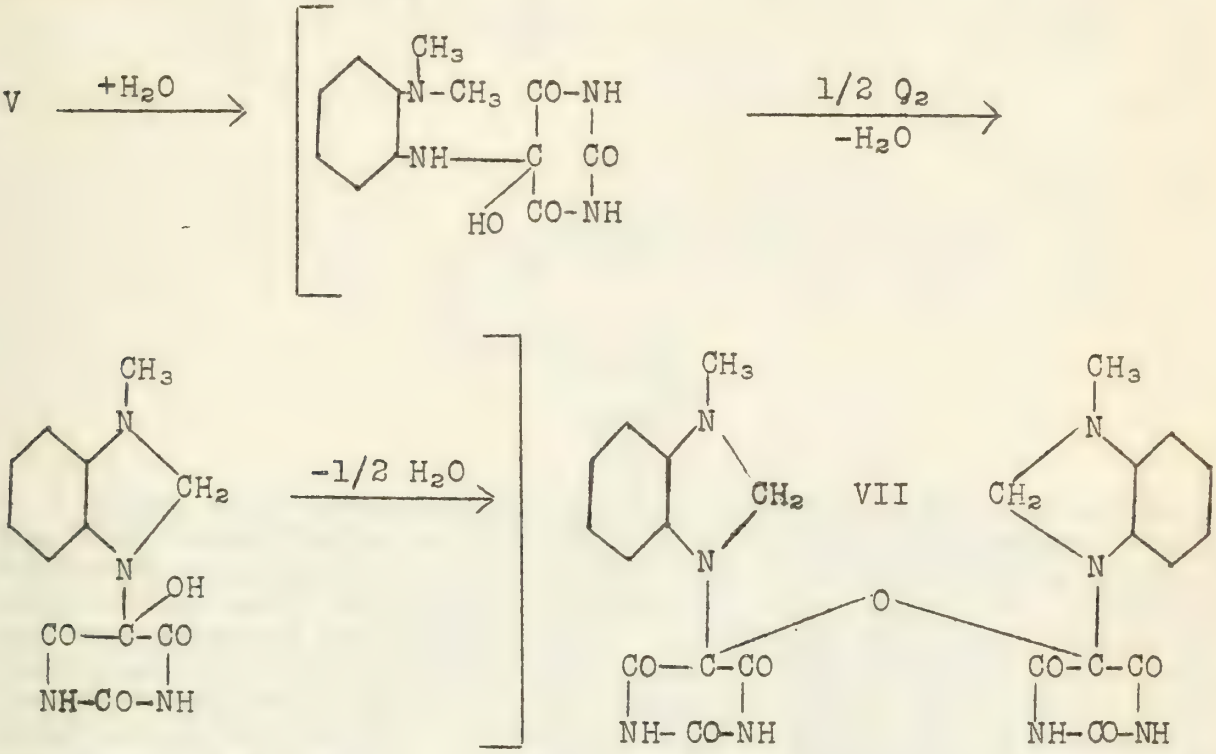
The dialuric acid derivative of type VI is amphoteric due to the amine and to the acidic -OH group on the dialuric acid rest. It reduces silver nitrate but gives no violet color with H_2O_2.HCl reagent since the position <u>para</u> to the dimethyl amino group is occupied.

Compound VI exists in a number of different easily interchangeable forms. This may be due to reversible hydrolytic splitting of one or both alloxan rests or the temporary addition of water to the >C=N- bond or possibly <u>cis</u>-<u>trans</u> isomerism even though this is not observed with simple anils.

The strong reducing ability of these anils as exemplified by alloxan-2-dimethyl amino anil is their most phenomenal property. A change occurs even with atmospheric oxygen and the reaction is considerable in the presence of H_2O_2. The end product of such

oxidation is a benzimidazole but the conditions may be controlled to obtain the intermediates.

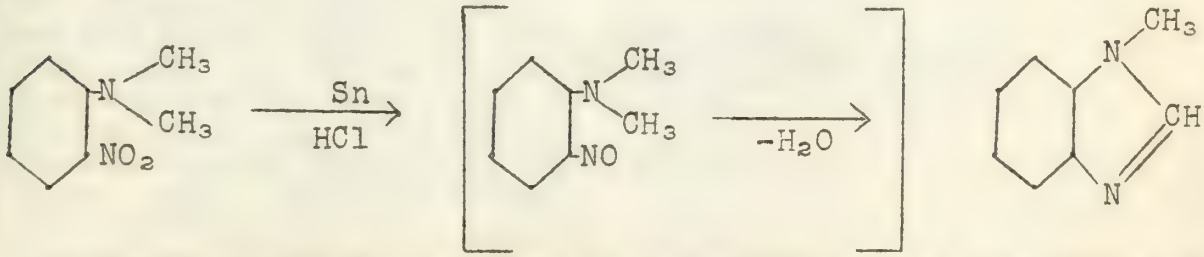
In neutral or acetic acid solution, oxygen may be passed through to give a weakly basic compound which is no longer sensitive towards oxygen but may be oxidized with peroxide to give the benzimidazole.



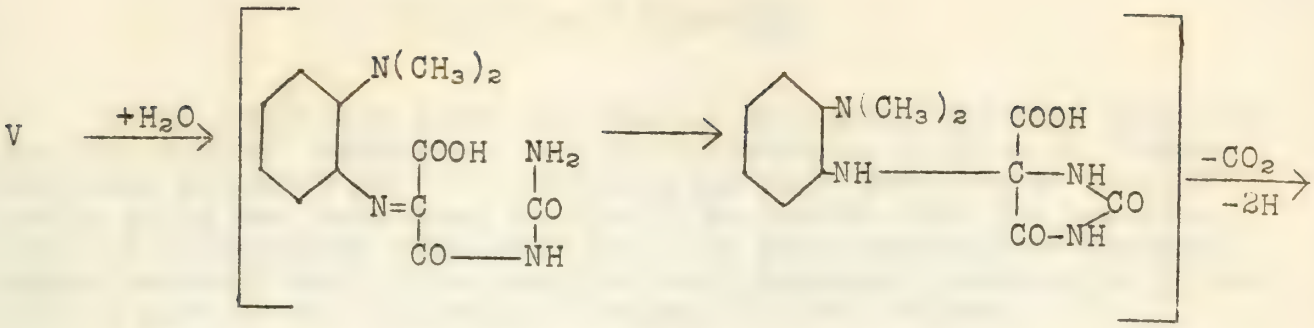
This bis-barbituryl ether (VII) then reacts with H_2O_2, the alloxan rest is oxidized to -COOH, from which CO_2 is split out. This product is then oxidized to produce 1-methyl-benzimidazole.

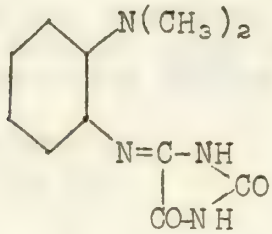
The oxidation to the bis-barbituryl ether occurs so easily with methyl groups on the benzene ring that it is formed merely on recrystallization from acetic acid.

This reaction shows a strong tendency for the formation of the imidazole ring. The reaction is most closely approximated by a ring closure of an o-dimethylamine on reduction with tin and hydrochloric acid.



Another unrelated method of oxidation occurs on warming the alloxan-2-dimethyl anil with dilute sodium carbonate solution and then decomposing with H_2O_2 and dilute acetic acid. Such a treatment of alloxan yields parabanic acid; likewise, the alloxan part of the anil is oxidized resulting in a parabanic acid derivative.





These reactions seem to shed some light on the influence of the ring substituents on the stability of aryl azomethines or anils. While the alloxan-4-dimethyl amino anil was easily hydrolyzed with even dilute acid, the ortho derivatives show stability toward dilute and concentrated acids and bases. Oxidation does not affect it, the most vigorous still leaving the >C=N- in the benzimidazole molecule. The dimethyl amino group in the ortho-position then offers this stabilizing influence. It has been long known that a phenolic-OH group exerts a similar influence in the resistance of benzylidine-p-amino phenol toward hydrolysis.

A partial explanation of the stability of these anils possibly comes from work showing cases where concentrated acid stabilized the >C=N- bond by the formation of a salt after addition of H_2O to the double bond had taken place.

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Reported by John C. Lawler
May 1, 1940.

REACTIONS OF HYDROGEN PEROXIDE

WITH ORGANIC COMPOUNDS

As an oxidizing agent in organic chemistry hydrogen peroxide has the unusual advantage that no nonvolatile residue is formed; reaction mixtures are not contaminated with troublesome metallic salts which are sometimes difficult to remove from the product. The use of metallic catalysts has only been extensively investigated recently and it is possible that hydrogen peroxide will become a more useful laboratory reagent in the future.

Reactions with Olefins.--Hydrogen peroxide does not react with olefins in the absence of a catalyst. In the presence of small amounts of osmium, vanadium, chromium, molybdenum, etc., salts and in nonaqueous solvents such as *tert*.-BuOH, *tert*.-AmOH, nitrites, and ethers. Hydrogen peroxide reacts with olefins as follows:

1. $R\text{-}CH{=}CH_2 \longrightarrow R\text{-}\underset{OH}{CH}\text{-}\underset{OH}{CH_2}$

The glycols formed may be further oxidized:

$$R\text{-}\underset{OH}{CH}\text{-}\underset{OH}{CH_2} \longrightarrow R\text{-}CHO + CH_2O \longrightarrow R\text{-}CO_2H + HCO_2H$$

2. $RR'C{=}CH_2 \longrightarrow RR'\underset{OH}{C}\text{---}\underset{OH}{CH_2} \longrightarrow RR'CO + HCHO$

3. $R\text{-}R'C{=}CHR'' \longrightarrow RR'\underset{OH}{C}\text{---}\underset{OH}{CHR''} \longrightarrow RR'\text{-}CO + R''CHO$

$$R''CHO \longrightarrow R''COOH$$

4. $RR'C{=}CR''R''' \longrightarrow RR'\underset{OH}{C}\text{---}\underset{OH}{CR''R'''} \longrightarrow RR'CO + R''R'''CO$

5. $CH_2{=}CH_2 \longrightarrow \underset{OH}{CH_2}\text{-}\underset{OH}{CH_2} \longrightarrow 2HCHO \longrightarrow HCO_2H$

6. $RC{\equiv}CH \longrightarrow \left[R\text{-}\underset{OH}{C}{=}\underset{OH}{CH}\right] \longrightarrow R\text{-}\underset{OH}{CH}\text{-}CHO$

$$\downarrow$$

$$[R\text{-}C(OH)_2\text{-}CH(OH)_2] \xrightarrow{-2H_2O} R\text{-}COCHO$$

$$R\underset{OH}{CH}\text{-}CHO \longrightarrow R\text{-}\underset{OH}{CH}\text{-}COOH$$

$$\downarrow$$

$$R\text{-}COCHO \longrightarrow R\text{-}COCOOH \longrightarrow R\text{-}COOH + CO_2 + H_2O$$

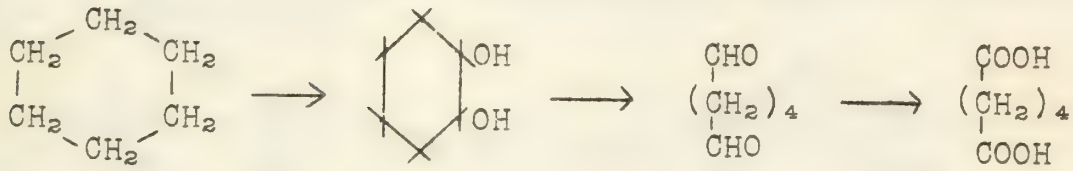
7. $R\text{-}C{\equiv}C\text{-}R \longrightarrow \left[R\text{-}\underset{OH}{C}{=}\underset{OH}{C}\text{-}R\right] \longrightarrow R\text{-}\underset{OH}{CH}\text{-}COR$

$$\downarrow$$

$$\left[R\text{-}C(OH)_2C(OH)_2\text{-}R\right] \xrightarrow{-2H_2O} R\text{-}COCOR$$

8. $HC{\equiv}CH \longrightarrow$ mixture of all of the possible products

9.



In all of these reactions good yields of the primary oxidation product can be obtained by controlling the quantities of hydrogen peroxide used.

Carbonyl Compounds.--

(a) Aldehydes

Formaldehyde is oxidized by hydrogen peroxide as follows:

$$2HCHO + H_2O_2 \longrightarrow 2HCO_2H + H_2$$

Other aldehydes are not oxidized easily but tend to form peroxides,

$$R\text{-}CHO + H_2O_2 \rightleftharpoons R\text{-}CH\begin{matrix}OH\\OOH\end{matrix}$$

$$R\text{-}CH\begin{matrix}OH\\OOH\end{matrix} + RCHO \rightleftharpoons R\text{-}\overset{OH}{C}H\text{-}O\text{-}O\text{-}\overset{OH}{C}HR$$

In either solution the hydroxyalkyl hydroperoxide forms readily and can be isolated. In a water solution the bis-(hydroxyalkyl) peroxide tends to be formed.

(b) Ketones

Acetone yields a trimeric peroxide when reacted with hydrogen peroxide in the presence of acid. Most other simple ketones yield dimeric peroxides under the same conditions.

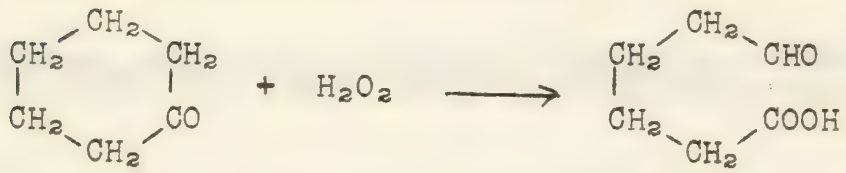
$$2C_6H_{10}O + 2H_2O_2 \xrightarrow[Ac_2O]{H_2SO_4} (C_6H_{10}O_2)_2 + 2H_2O$$

cyclohexanone

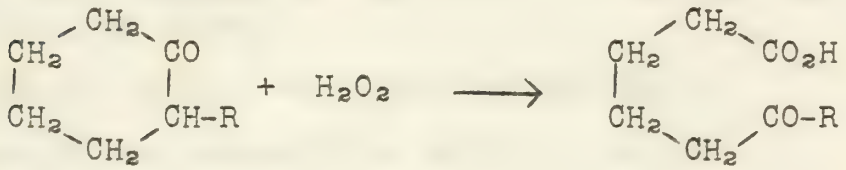
Treatment of these peroxides with acids yields the original ketone and hydrogen peroxide.

(c) Cyclic Ketones

Cyclohexanone when treated with 30 per cent H_2O_2 and concentrated sulfuric acid yields polymeric ω-hydroxycaproic acid. In the presence of a little pervanadic acid cyclohexanone is oxidized to the half aldehyde of adipic acid.



Likewise,



Although aldehydes are much more easily attacked than cyclic ketones by most oxidizing agents, hydrogen peroxide has less effect on them.

(d) α-Diketones

$$R\text{-}COCOR + H_2O_2 \longrightarrow 2RCO_2H$$

(e) α,β-Unsaturated Ketones

$$R\text{-}CH{=}CH\text{-}CO\text{-}R + H_2O_2 \xrightarrow{\text{alkali}} R\text{-}\underset{\diagdown O \diagup}{CH\text{-}CH}\text{-}CO\text{-}R$$

Neither unsaturated hydrocarbons nor ketones react with hydrogen peroxide under similar conditions.

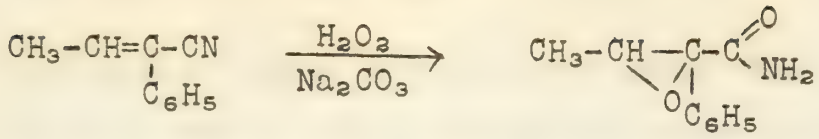
(f) α-Keto Acids

$$R\text{-}COCO_2H + H_2O_2 \longrightarrow R\text{-}CO_2H + CO_2$$

<u>Reaction with Nitrites</u>.--In alkaline solution hydrogen peroxide smoothly hydrolyzes nitrites to the corresponding acid amides.

$$R\text{-}CN + H_2O_2 \xrightarrow[\text{NaOH}]{\text{dilute}} R\text{-}C{=}O{-}NH_2$$

With unsaturated nitrites:



In the presence of a small amount of ferric chloride nitrites are oxidized to hydroxamic acids which give a typical cherry red color in the presence of the iodine salt. Amides are more easily oxidized than amines in acid solution.

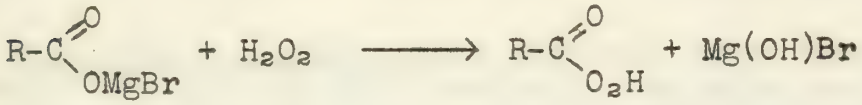
Reactions with Organomagnesium Compounds.--Hydrogen peroxide in dry ether solution reacts with the Grignard reagent to form alcohols.

$$RMgBr + H_2O_2 \longrightarrow R\text{-}OH + Mg(OH)Br$$

With organomagnesium derivatives of amines substituted hydroxylamines are formed.

$$RNHMgBr + H_2O_2 \longrightarrow RNHOH + Mg(OH)Br$$

Peracids are formed from salts of acids:



Reactions with Amines.--Secondary amines form disubstituted hydroxylamines when treated with hydrogen peroxide and tertiary amines form amine oxides.

$$R_2NH + H_2O_2 \longrightarrow R_2NOH + H_2O$$

$$R_3N + H_2O_2 \longrightarrow R_3N{\rightarrow}O + H_2O$$

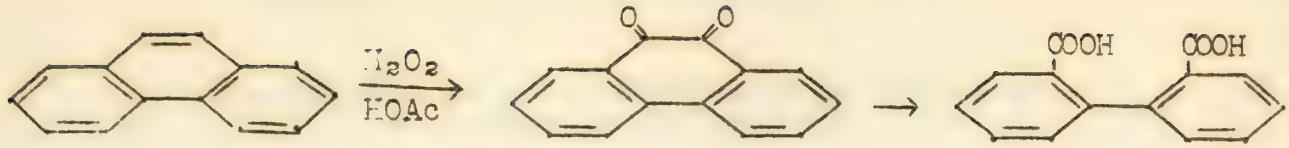
The reaction to form amine oxides has been used in the study of alkaloids.

Reactions with Aromatic Compounds.--Benzene reacts with hydrogen peroxide in the presence of ferrous sulfate to form phenol in 15-20 per cent yields.

Hydrogen peroxide oxidizes phenol to catechol in 20-30 per cent yields in the presence of ferrous sulfate.

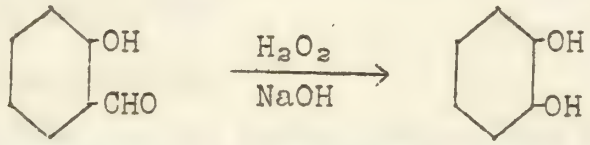
Naphthalene dissolved in acetic acid yields phthalic acid as the only identifiable product.

Phenanthrene yields phenanthrene quinoin and then diphenic acid.



Anthracene yields anthraquinone under similar conditions.

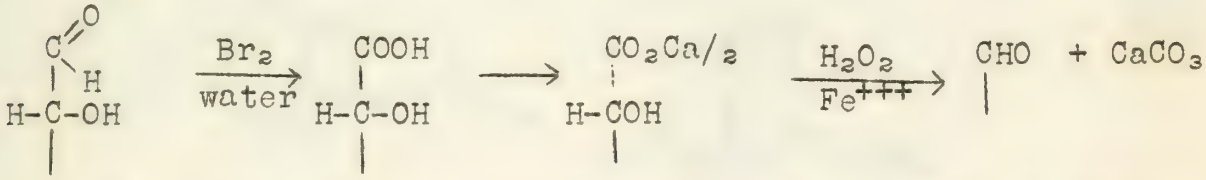
Catechol may be conveniently prepared by the action of alkaline hydrogen peroxide upon salicylaldehyde. This is a general reaction for o- or p-hydroxyaldehydes.



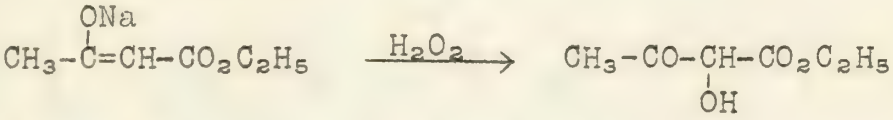
Reactions with Organic Sulfur Compounds.--In acid or neutral media mercaptans are oxidized to disulfides and thence to sulfonic acids.

In basic media most sulfur compounds in which the sulfur atom is not in a stable ring are oxidized to the corresponding oxy compounds and the sulfur is quantitatively oxidized to sulfate. This method provides a good micro method for the determination of sulfur compounds.

Miscellaneous Reactions.--The well known Ruff degradation of sugars is perhaps the best available for this purpose. The sugar is oxidized to the corresponding acid with bromine water and the calcium salt of this acid is treated with hydrogen peroxide in the presence of a trace of ferric ion.



The sodium salt of autoacetic ester is oxidized to ethyl α-hydroxy acetoacetate.



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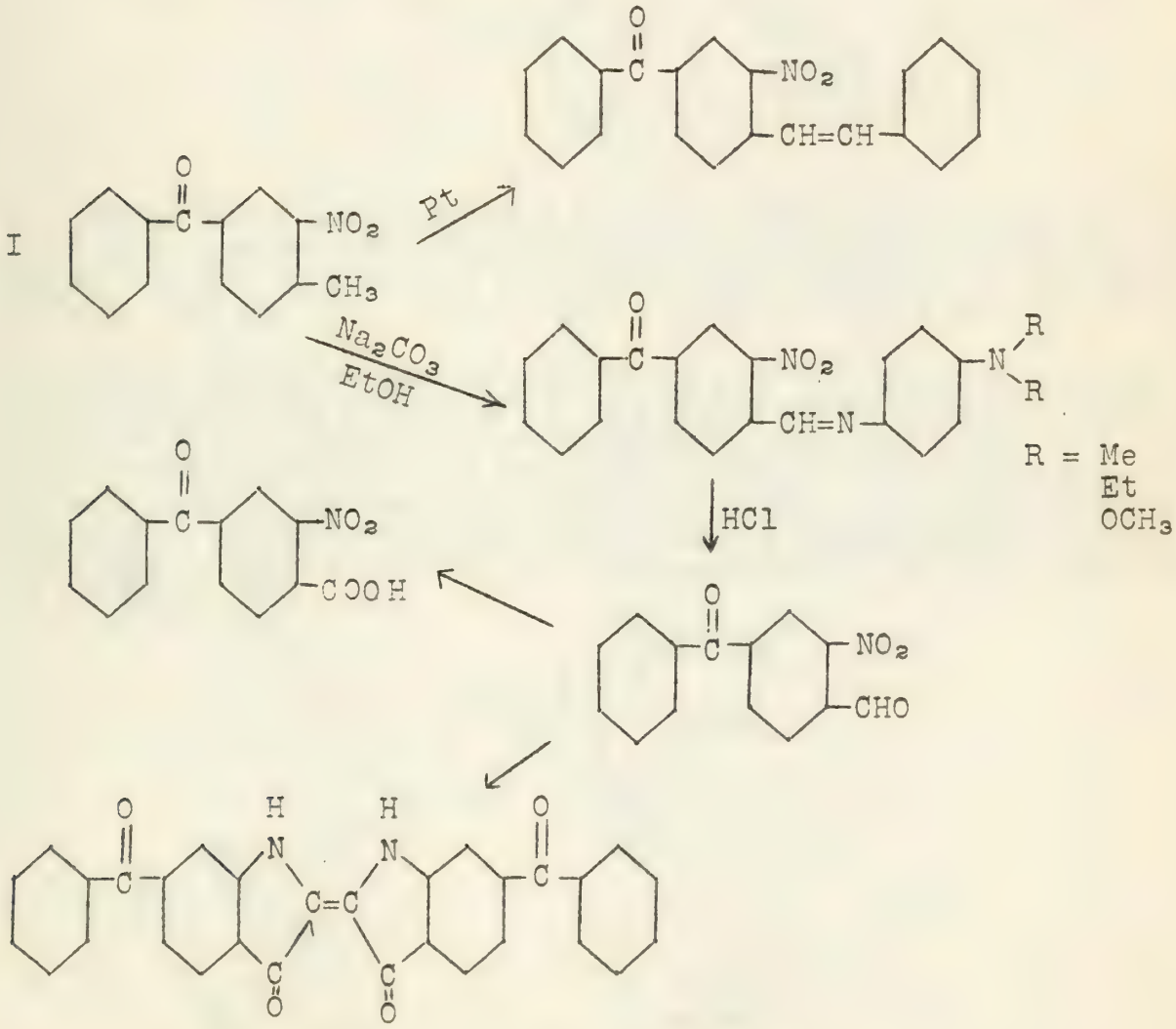
Reported by M. D. Armstrong
May 8, 1940.

Chardonnens et al -- Institute de Chemie de
l'Universite de Fribourg

It has been known for some time that the methyl group in 2,4-dinitrotoluene is sufficiently active to undergo certain types of condensations. This has been shown by the formation of stilbene and azomethine derivatives. Other negative groups such as CN, COOEt and SO_2NH_2 may be substituted for one of the NO_2 groups and still cause the methyl group to show enough activity to condense with aromatic aldehydes.

I Benzoyl Derivatives

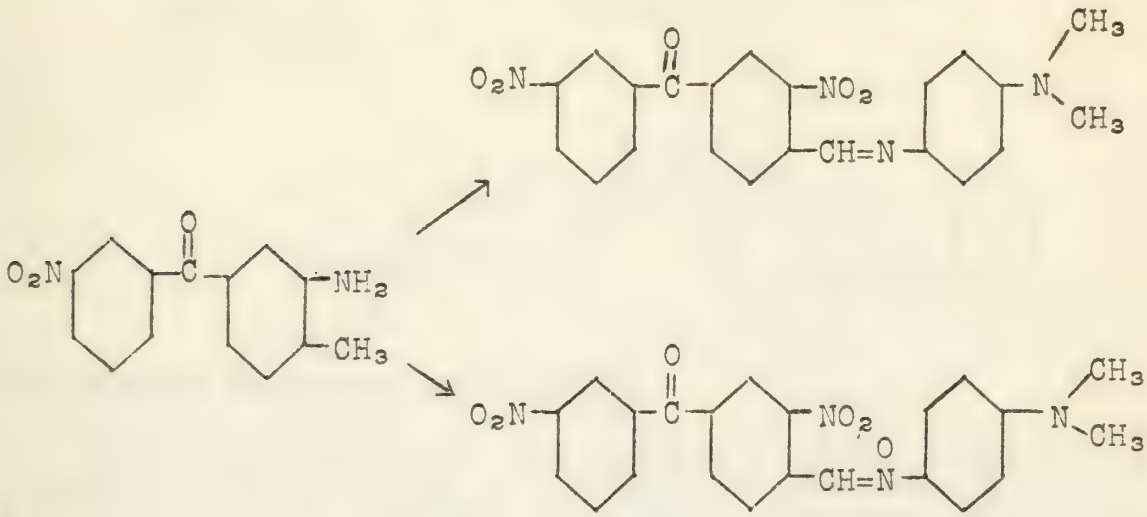
In addition to the above groups, the benzoyl group also favors the reactivity of the methyl group.



This reaction has been extended to the following compounds.

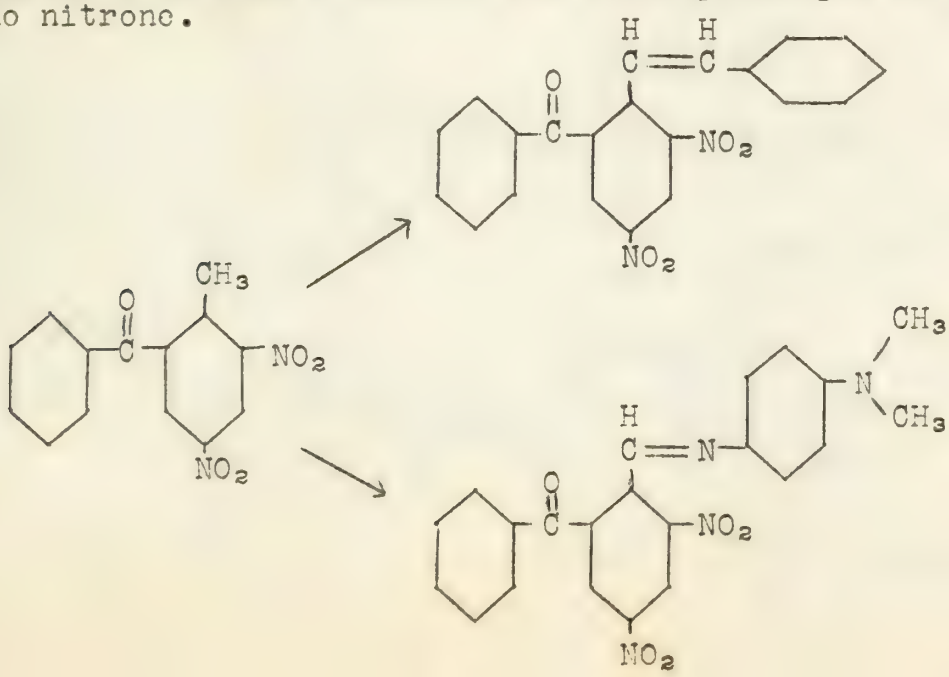
II 4-Methyl 3,3'-dinitrobenzophenone
III 4-Methyl 3,5-dinitrobenzophenone
IV 4-Methyl 3,5,3'-trinitrobenzophenone

These compounds condense with aromatic aldehydes without difficulty; the methyl group showing a reactivity very similar to that of compound I. In the condensation of compound II with p-nitrosodimethylaniline, in addition to the normal azomethine, a nitrone is also formed.

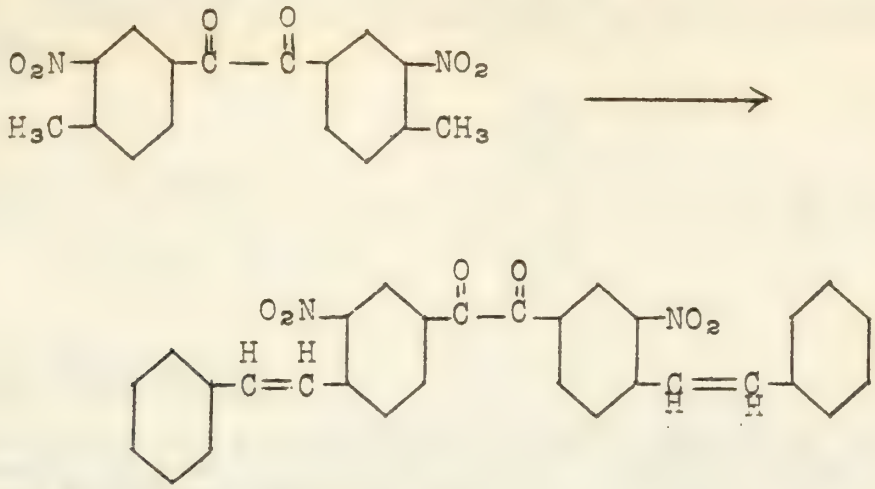


This being an unexpected reaction, the condensation product of I with p-nitrosodimethylaniline was reinvestigated and a small amount of the nitrone was isolated. With compound II the azomethine was the only product which could be identified.

When the nitro and benzoyl groups in I were interchanged the reactivity of the methyl group was found to be considerably less. It would not condense with benzaldehyde, but did react with p-nitrosodimethylaniline to give low yields of the corresponding nitrone. When another nitro group is added, the reactivity of the methyl group is increased and readily condenses with benzaldehyde to form a styrene and correspondingly an azomethine but no nitrone.



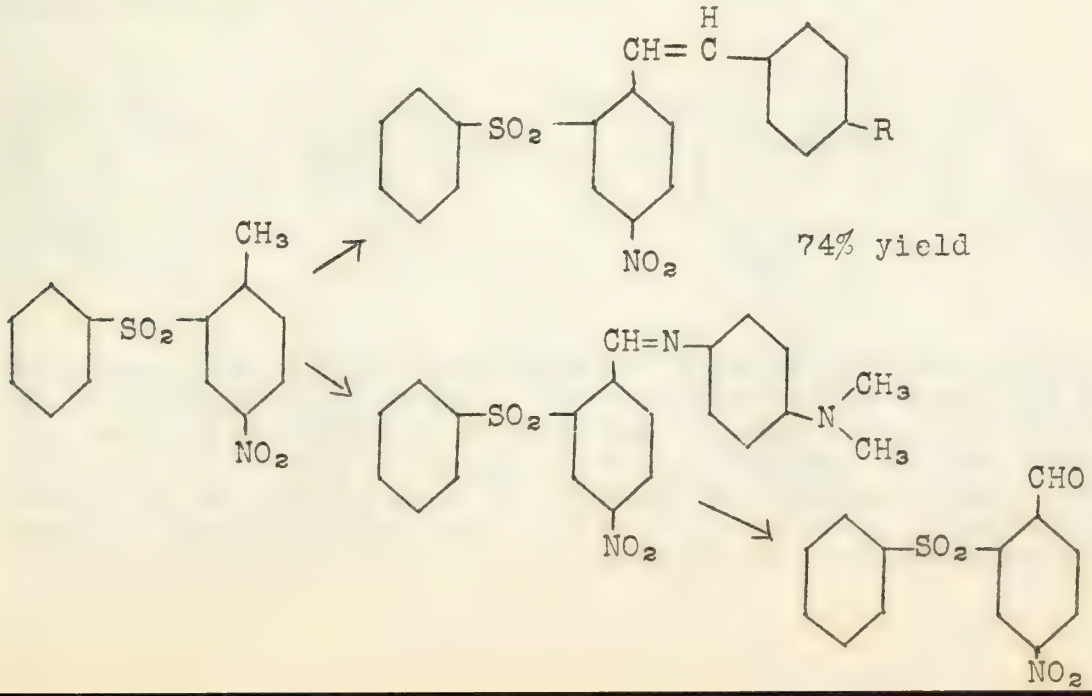
Analogous reactivity is shown in 4,4'-dimethyl 3,3'-dinitrobenzil. It condenses with benzaldehyde and with o-phenylenediamine.



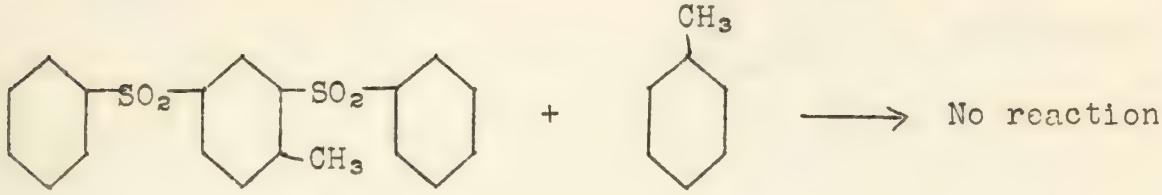
II Benzene Sulphonyl Derivatives

The determination of the reactivity of the methyl group was extended by substituting a sulphonyl for the benzoyl group. 2-Nitro-4-benzene sulphonyl toluene was prepared and readily entered into all the reactions shown above. Similarly the 4,4'-dimethyl 3,3'-dinitrodiphenyl sulphone formed a distyryl and reacted with two mols of p-nitrosodimethylaniline to form the bis-p-dimethylamino anil which in turn is readily hydrolyzed to the dialdehyde.

As in the case of the benzoyl derivative, the position of the sulphonyl and nitro were interchanged, and based upon the results obtained previously, it was expected that the compound would be quite inert. On the contrary it condensed rapidly with benzaldehyde and p-nitrosodimethylaniline to give good yields of the styrene and azomethine. The latter reaction also differs from the benzoyl derivative as there a low yield of the nitrone was obtained.



Two sulphonyl groups were introduced but the compound proved to be very inert and has been compared to 2,4-dicyanotoluene in this respect.

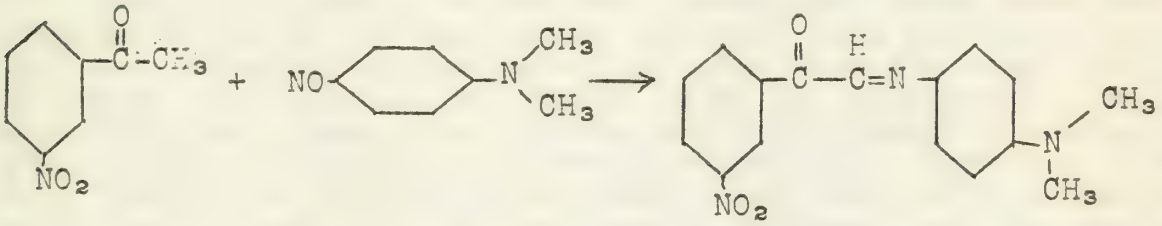


III Acetyl Derivatives

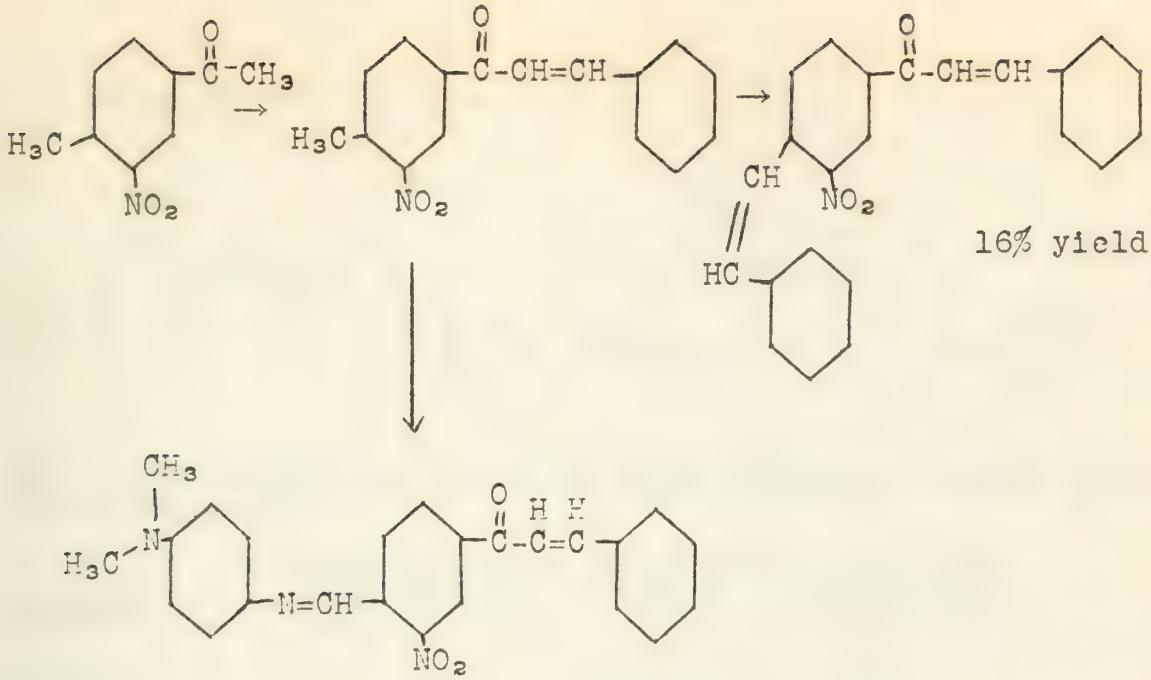
Continuing the substitution of other groups in dinitrotoluene the 4-acetyl derivative was prepared. However, here it is to be remembered that the choice of reactions by means of which one is able to test the reactivity of the methyl group, is quite limited. For example, it is known that acetophone reacts with benzaldehyde under varied conditions to form a chalcone. However, no reaction with nitroso derivatives has been observed, but here with sufficiently active nuclear methyl group condensation should occur with p-nitrosodimethylaniline.

The reaction between 4-methyl-3-nitroacetophenone and p-nitrosodimethylaniline gave a very complex mixture. The results of analyses of various fractions showed that the two methyl groups entered into the reaction and, therefore, the reactivity of the lateral methyl group is due to the presence of the nitro group. To confirm this the reactivity of the isomeric nitroacetophenones was studied.

The 3-nitroacetophenone reacted with p-nitrosodimethylaniline to give a very impure product. By chromatographic methods a small amount of the corresponding anil was isolated.



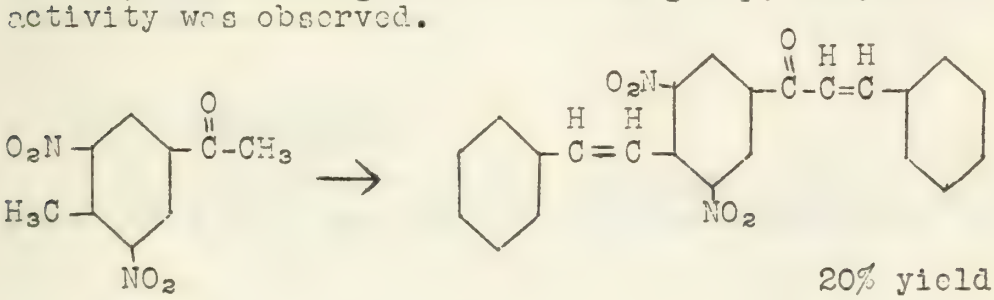
Similarly the 4-nitroacetophenone forms ω-p-dimethylamino anil of 4-nitrophenyl glyoxal. The 2-nitroacetophenone did not react, the only product being formed was the 4,4'-bis-dimethylamino azoxybenzene. As a result of these findings it is evident that there is no possibility of testing the reaction capacity of the nuclear methyl group due to the acetyl group. However, the chalcone which is formed does undergo the expected reactions.



16% yield

40% yield

By introducing another nitro group, very little increase in activity was observed.

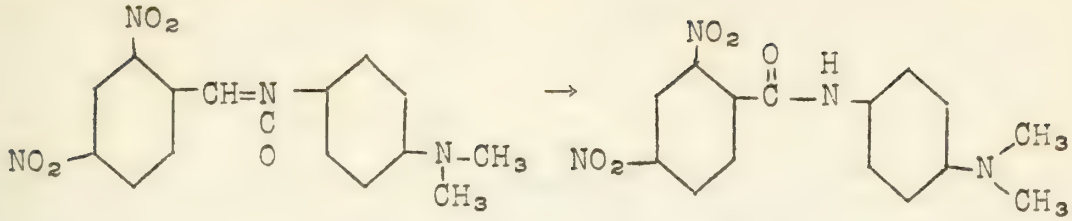


20% yield

IV <u>Isomeric Nitrotoluenes</u>

Previous attempts to condense mononitrotoluene have been unsuccessful but it has been shown recently that p-nitrotoluene will form substituted stilbenes and azomethines in very low yields. The ortho compound will not react under any conditions. As has been mentioned above, the dinitro derivative readily condenses with nitroso compounds and aromatic aldehydes. When one of the nitro groups is replaced by a cyanide the reactivity of the methyl group is retained. It was originally reported that the reaction between p-nitrosodimethylaniline and 2,4-dinitrotoluene gave a nitrone. Later investigators reported the formation of the azomethine. When this reaction was repeated by the authors and the product subjected to chromatographic analysis, both condensation products were found to be present. Subsequent work then showed that the formation of either compound depended mainly upon the experimental conditions. Slight variations caused either the nitrone or the azomethine to predominate. The mechanism of this reaction is still in doubt. It was presumed that the nitrone was the intermediate, but when the pure mixture was subjected to the same conditions as that of the condensation, it was found to

rearrange to the anilide.

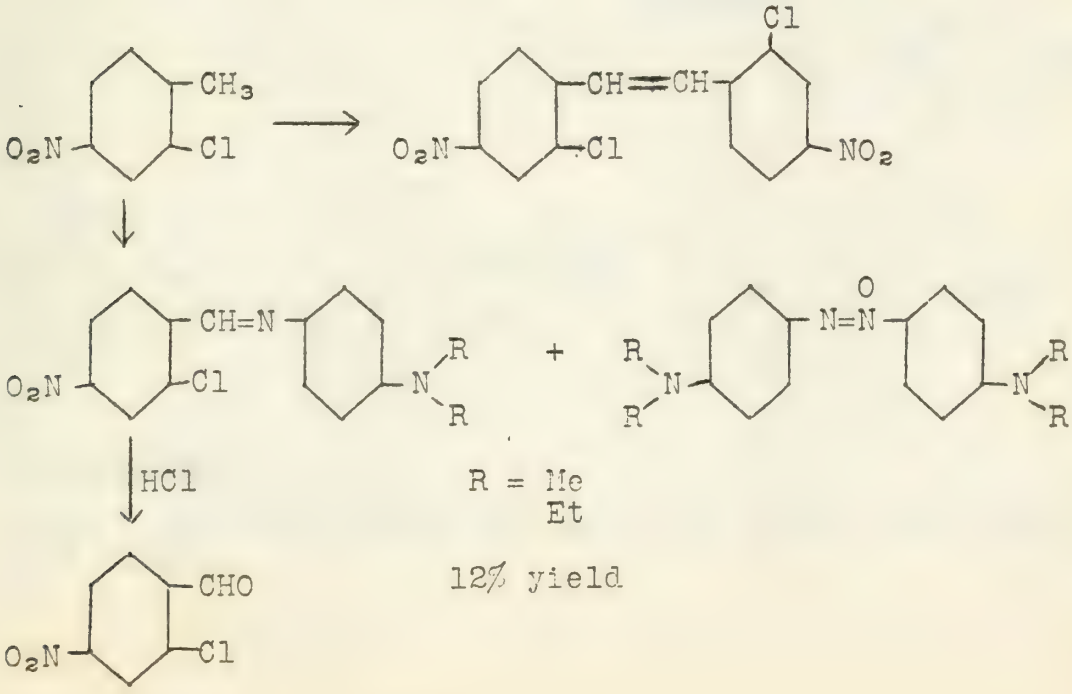


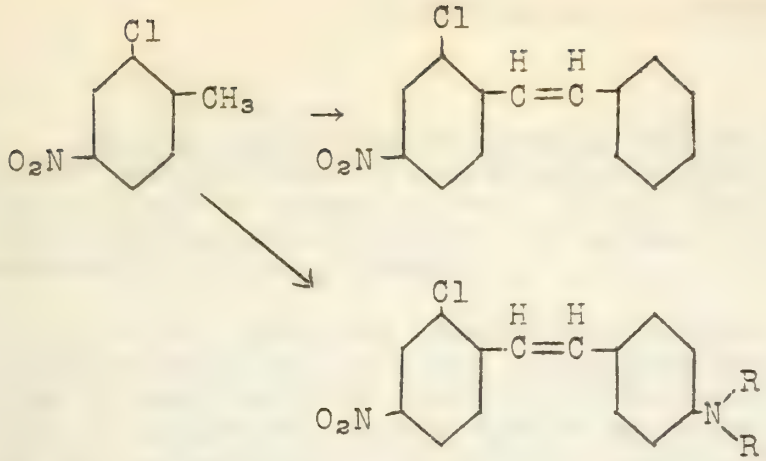
The reactive capacity of other nitrotoluenes is shown in the following table.

Toluene	$(CH_3)_2NC_6H_4NO$ %	C_6H_5CHO %	$(CH_3)_2NC_6H_4CHO$ %
2-nitro	-	-	-
4-nitro	1.5	3.5	22.0
2,3-dinitro	-	-	-
2,4-dinitro	83.0	90	71
2,5-dinitro	-	16	14
2,6-dinitro	1	33	55
3,4-dinitro	9	-	-

V Other Derivatives

The following equations represent some of the reactions which have been carried out on other derivatives of nitrotoluene.

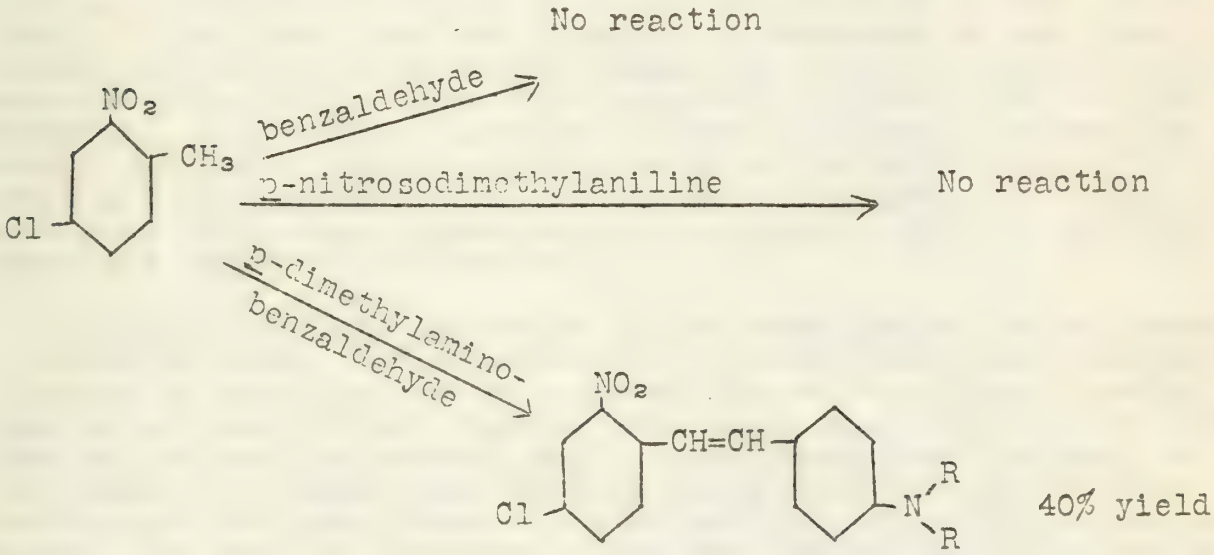




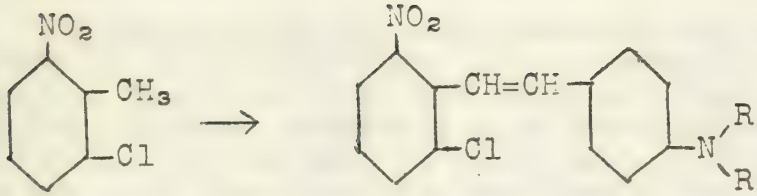
14% yield

89% yield

The chlorine here may be replaced by bromine or iodine to give slightly better yields



40% yield



6% Yield

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Helv., 16, 1295 (1933); 22, 823, 853, 1278, 1471 (1939); 23, 292 (1940).

Reported by L. A. Brooks
May 8, 1940

CHROMATOGRAPHIC ADSORPTION

Historical:--Chromatographic adsorption is a method which was first used in 1906 by the Russian botanist Tswett in a study of the pigment of green leaves. After that time it was used by a few investigators who utilized the method for the separation of small amounts of plant pigments.

In 1931 Kuhn and Lederer and others demonstrated that chromatography could be used for the separation in satisfactory quantities of many natural products which would otherwise be very difficult to separate. Since that time Tswett's method has been used for the separation, purification and estimation of many colored and colorless compounds.

Method:--A vertical tube is filled with a finely powdered suitable chosen adsorbent, and a solution of the material to be investigated is filtered through, usually with the aid of suction although sometimes by means of an excess pressure at the top of the tube. It is found that the pigments are adsorbed in the form of colored zones forming a chromatogram. In order to separate the zones satisfactorily it is then necessary to "develope" the chromatogram. To do this a suitable solvent is passed through the column until the colored portion occupies the whole tube. The zones are then separated by cutting up the column, the content of each zone being then extracted with a suitable solvent, and the adsorbent removed by filtration.

Tubes:--The size and shape of the tubes depend on the amount of material used. For adsorption in aqueous media where filtration may be slow one may use a short tube with a large diameter such as a glass Buchner funnel. For large quantities a very large tube may be used or several small ones. Sometimes the tube is surrounded by another tube through which water can flow from a heater when the adsorption is to be carried out at higher temperatures. The smaller adsorption tubes are closed at the bottom by a plug of cotton, and the larger tubes with a porous plate.

Adsorption Media:--In principle one can use any finely powdered or fibrous material as adsorbent, provided that it is insoluble in the solvent and does not react either with the solvent or the adsorbed compounds in a troublesome manner. The extent and nature of the surface is important. If the adsorbent is too active, it may hold the adsorbed substances too strongly. Sometimes several adsorbents are used one above the other in the tube. Sometimes one employs a mixture of different adsorbents or a mixture of different grades of the same adsorbent. The particle size varies from 1.5 to 10 u. The finer the grain, the more intense is the adsorption. However, if the grain is too fine, the adsorption is too intense and filtration is retarded. The adsorbent may be activated in various ways. Thus alumina has been activated by washing with tap water or by treating with hydrochloric acid.

Examples:--For the extract from green leaves sugar, calcium carbonate and alumina are placed in order from top to bottom of the tube. It is found that the sugar adsorbs the chlorophyls, calcium carbonate the xanthophyls, and alumina the carotens.

Mixtures:--A mixture of magnesia and silica is useful for the carotenoids. A mixture of alumina and carbon has been used for the separation of ergosterol and sitosterol.

Commonly Used Adsorbents:--

Powdered sugar	Fuller's earth
Al_2O_3	Na_2SO_4
MgO	Talc
$Ca(OH)_2$	Kieselguhr
CaO	Kaolin
$CaSO_4$	Silica gel
$CaCO_3$	

Solvents:--The choice of a suitable solvent depends largely on the solubility. Water is usually avoided since the filtration is likely to be very slow and some of the adsorbent is likely to be dissolved. Also a small change in the hydrogen ion concentration can invert the order of the zones in the column. Usually a nonpolar organic solvent is used. The best solvents boil between 40° and 80°. High boiling solvents should not be used, if in connection with the experiment a sensitive substance has to be isolated from the filtrate. The chief solvents are:

Carbon bisulfide.
Petroleum Ether. This is the most useful solvent.
Benzene. This is also often used. It is distinguished from petroleum ether in many cases in that it is a stronger extractant. It is often used mixed with petroleum ether.
$CHCl_3$, CCl_4, CH_2Cl_2 and ether are used. Ether must be free from peroxides.

Extractants:--Here polar solvents are used such as methyl and ethyl alcohol and acetone. Often a mixture of the original solvent with 0.5% to 2% alcohol can be used. If the chromatography must be repeated with a part of the column it is convenient to extract with a weak methyl alcohol solution in petroleum ether, filter, extract the alcohol with water, dry and pour through a fresh column. As a last resort in the case of acid insensitive substances adsorbed on calcium carbonate, one can dissolve the adsorbent in hydrochloric acid thus leaving the adsorbed substance behind. If adsorbed on sugar, the adsorbent can be dissolved with water.

Filling of the Tube:--One first introduces at the bottom of the tube a plug of cotton or a porous plate, adds the adsorbent in small quantities and packs down well with a wooden pestle using a gentle suction. For larger tubes a suspension may be

made in a suitable solvent which is then filtered through the column with suction. It is important that a uniform well-packed column be formed.

Some of the pure solvent is then filtered through the tube using a slight suction, and then one adds the solution of the substance to be investigated, usually through a dropping funnel.

Development of the Chromatogram:--Here one pours through the column a solvent which may either be the same as the original solvent or not. In this process the colored zones widen out and extend further down the tube.

Removal and Separation of the Column:--The column must neither be too moist nor too dry. The removal of the column may be carried out by shoving it out of the tube with a wooden pestle onto a piece of paper. The various zones may then be separated with a knife or spatula. The column may also be cut up mechanically. Sometimes some of the lower zones are removed in the development by passing through solvent until these zones pass one after the other into the filtrate.

Adsorption of Colorless Compounds:--Here special methods must be used for the marking of the zones.

(a) Transform the material into colored derivatives which can then be adsorbed in the usual manner. This has been done in the case of ketones which were adsorbed in the form of their dinitrophenylhydrazones.

(b) Examination of the chromatogram in ultraviolet light.

(c) By the use of color reactions. For example, the naphthol sulfonic acids were separated by adsorption on alumina and development with water. On continuing the development with water, the acids pass one at a time into the filtrate where they may be detected with a diazonium solution which gives different colors with each of the acids.

A modification of this idea is to press out the column from the tube and to paint a streak along the axis of the tube with a suitable indicator.

Relationship between Chromatogram and Constitution:--

Double Bonds: In related compounds the adsorption is increased
(1) If the number of double bonds is increased.
(2) If with the same number of double bonds, all are conjugated.
(3) If in the case of identical unsaturated compounds, hydroxyl groups are introduced. The adsorption increases with the number of hydroxyl groups.
(4) If a conjugated carbon-carbon double bond is replaced by a conjugated carbonyl.

Examples:

Diphenyl polyenes--Here it is found that diphenyl octatetraene is more strongly adsorbed than the hexatriene, this than the butadiene, etc.

Indolenine dyes--These are adsorbed in the following order.

Indolenine blue	11 F
Indolenine violet	10 F
Indolenine red	9 F
Indolenine yellow	8 F

Natural polyene hydrocarbons--The following are adsorbed in the following order.

Lycopin	11 F conjugated and 2 F isolated
γ-Caroten	11 F conjugated and 1 F isolated
β-Caroten	11 F conjugated and 0 F isolated
α-Caroten	10 F conjugated and 1 F isolated

Polynuclear aromatic compounds--

1,2-Benzpyrene	5 rings	10 F
Chrysene	4 rings	9 F
Pyrene	4 rings	8 F
Phenanthrene	3 rings	7 F

Hydroxyl Groups:--Alcohols are more strongly adsorbed than are the corresponding hydrocarbons. Cryptoxanthine is more strongly adsorbed than β-caroten from which it varies only by a hydroxyl group. When the hydroxyl groups are esterified, the adsorbability decreases.

Nonenolizable carbonyl groups have less affinity for the adsorbent than hydroxyl groups. Thus rhodoxanthine, $C_{40}H_{50}O_2$, with two carbonyl groups is less strongly adsorbed than is zeaxanthine, $C_{40}H_{56}O_2$ which is more saturated and contains two hydroxyl groups.

Stereoisomers:--Certain cis-trans isomers have been separated by this method such as cis- and trans-crocetine.

Henderson and Rule have attained a complete resolution of p-phenylene bis-iminocamphor by adsorbing on an optically active adsorbent, d-glucose. The d-isomer is more readily adsorbed than its antipode.

Applications:--Chromatographic adsorption has been applied chiefly to the separation and purification of closely related natural products and their degradation products. These would be very difficult or impossible to separate by means of solubility differences.

This method has been used for the separation of complex polynuclear hydrocarbons such as carcinogenic hydrocarbons, natural pigments such as cyanine dyes, chlorophyls, terpenes, carotenoids, sterols, hormones, porphyrins, alkaloids, vitamins, etc.

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Reported by B. D. Deacon
May 15, 1940

THE NAPHTHENIC ACIDS

The naphthenic acids may be defined as the cyclic carboxylic acids found in and obtained from petroleum. The acidic material present in petroleum is partly phenolic and partly carboxylic. The carboxylic acids are aliphatic or naphthenic or a mixture of the two, depending on the source of the petroleum.

The naphthenic acids have been studied very thoroughly, both as a means of determining the constitution of petroleum and as a potential raw material. The problem of the origin of the naphthenic acids is complicated by the fact that the high molecular weight acids are cracked to lower molecular weight by the distillation of the petroleum, the alkaline wash treatment and the concentrated sulfuric acid raffination. However, it has been shown that the naphthenic acids are a primary constituent of the crude oil.

There are two theories of their origin that have some backing:

1. The naphthenic acids are formed at the same time and from the same materials as the hydrocarbons.

2. The naphthenic acids are formed by air oxidation of the parent hydrocarbons.

Petrov has shown that both processes are involved.

Table

Source	Per cent Naphthenic Acid
Russian	0.07 -0.20
Russian Baku	1 - 3
Texas	0.03
California	1.00
Pennsylvania	0.03
Japanese	13
Rumanian	5

The animal output has been estimated at 50,000 tons.

Extraction.--The petroleum alkali bottoms are diluted and distilled at reduced pressure. The residual alkaline solution may then be solvent extracted. The aqueous solution is acidified, the separated acids distilled. The distilled acids may be solvent extracted to remove nonacidic material.

Solvent purification of petroleum also yields naphthenic acids.

Purification.--The complete separation of hydrocarbons, phenolic material, and aliphatic acids is apparently never attempted commercially. For analytical purposes Von Braun and others found that none of the extraction methods were quantitative. The phenolic material can be removed by selective esterification and subsequent extraction of the unesterified phenols with alkali. The hydrocarbons are best removed by conversion of the naphthenic acids to derivatives. Repeated fractionation of the ester and amine derivatives gave fractions of 1-2° ranges which still were complicated mixtures of isomers. The aliphatic acids are removed by distillation.

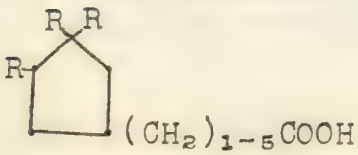
Structure.--The structure of the naphthenic acids is based on reactions of mixtures of acids and isolation of pure acids.

Empirical Formulas

$C_nH_{2n}O_2$	$< C_8$
$C_nH_{2n-2}O_2$	C_8-C_{12}
$C_nH_{2n-4}O_2$	$C_{13}-C_{23}$
$C_nH_{2n-6}O_2$, $C_nH_{2n-8}O_2$, $C_nH_{2n-10}O_2$	$> C_{23}$

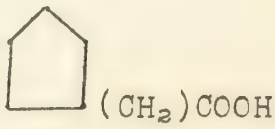
Reactions;--(a) No unsaturation, therefore cyclic acids; (b) Zelinski dehydrogenation is negative, therefore contains no 6-membered rings; (c) Skraup test negative, therefore carboxyl not directly attached to ring; (d) Chlorine number averages 2, therefore carboxyl attached to methylene group; (e) Von Braun degradation indicates length of chain as $-(CH_2)_{1-5}$; (f) Bicyclics consist of two separate rings; (g) Acid number and molecular weight indicate monobasic acids; (h) Same naphthenic acids present in all crudes; (i) Isolated acids relate petroleum to cellulose.

Pure Acids.--

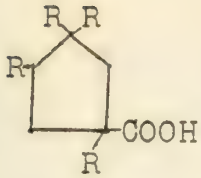


I

II
camphonanic acid



III



V (?)

VI

[R = CH_3]

Methods.--

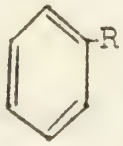
1. $RCH_2COOH + C_2H_5OH \xrightarrow{HCl}$ 92 per cent $RCH_2COOC_2H_5$

$\downarrow$ Na + C_2H_5OH

88 per cent $RCH_2CH_3 \xleftarrow[HCl]{Zn + HOAc} RCH_2CH_2X \longleftarrow$ 70 per cent RCH_2CH_2OH

$\uparrow$ 88 per cent P + I_2

2. Zelinski dehydrogenation

6-carbon ring $\xrightarrow[300^\circ]{Pt}$ H_2 + 

other rings $\longrightarrow$ no H_2

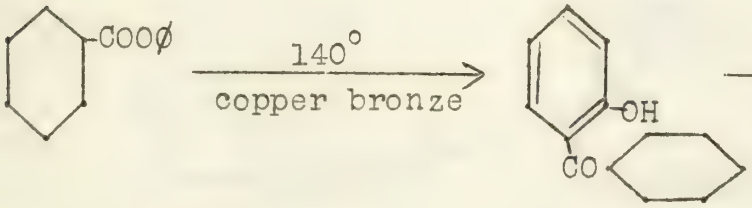
3. Chlorine number

$RCH_2CONHR \xrightarrow{PCl_5} RCCl_2CONHR$

$R_2CHCONHR \longrightarrow R_2CClCONHR$

$R_3CCONHR \longrightarrow R_3CCONHR$

4. Skraup test



$\longrightarrow$ dimroth Bonc ester reaction

5. Von Braun degration

$RCH_2COOH \longrightarrow RCH_2COOC_2H_5 \longrightarrow RCH_2CH_2OH$

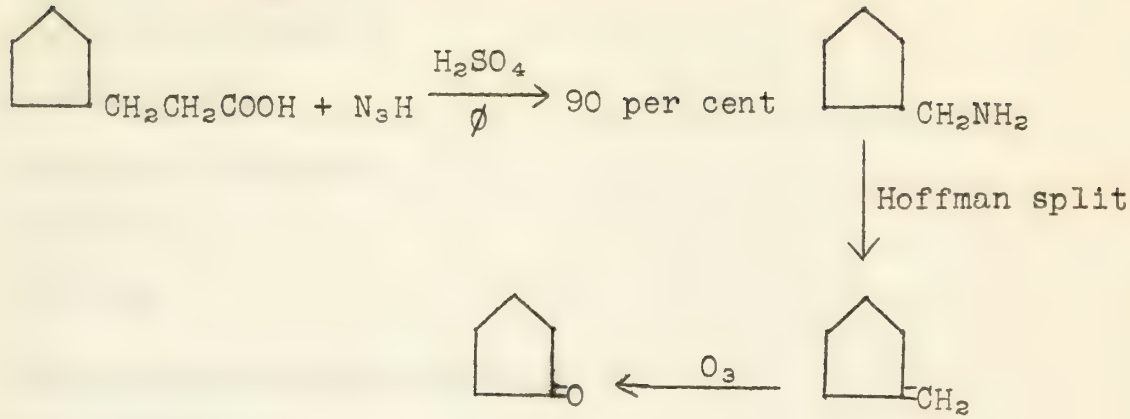
$\downarrow$ P + Br_2

$RCH{=}CH_2 \xleftarrow[split]{Hoffman} RCH_2CH_2\overset{(CH_3)_3}{\underset{Br}{N}} \xleftarrow{(CH_3)_3N} RCH_2CH_2Br$

$\downarrow O_3$

$RCHO \longrightarrow RCOOH$

6. K. F. Schmidt amination



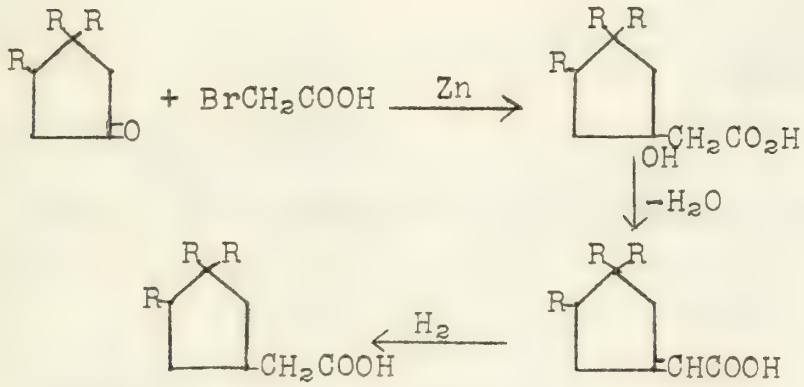
7. $RNHCO\emptyset + PCl_3 + Br_2 \longrightarrow$ 50 per cent $RBr + \emptyset CN$

8. $RCH_2Br + CH_2(COOC_2H_5)_2 \longrightarrow RCH_2CH(COOC_2H_5)_2$

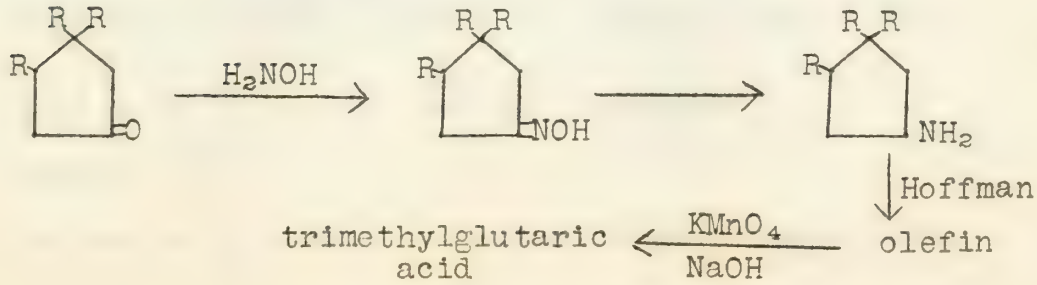
$\downarrow CO(NH_2)_2$

$RCH_2CH(CO{-}NH)_2C{=}O \longrightarrow RCH_2CH_2COOH \longrightarrow RCOOH$

9.



10.



11. Selective esterification
    Selective hydrolysis
    Selective amidation

12. Aniline point

13. Specific dispersion

14. Viscosity

15. Density

<u>Derivatives and Reactions</u>.--

1. Acid anhydrides

$$\text{acid} \xrightarrow[Ac_2O]{} (RCO)_2O$$

$$\text{acid} + CH_2{=}C{=}O \longrightarrow \text{mixed anhydride}$$

$$\text{salt} + COCl_2 \longrightarrow (RCO)_2O$$

2. Carbonyls

$$\text{acid} \xrightarrow[410^\circ]{MnO,\ ZnO} \text{ketones}$$

$$\text{acid} + Cl_2 \longrightarrow \alpha\text{-}Cl + \text{alkali} \longrightarrow \alpha\text{-}OH \xrightarrow{\text{distillation}} -CHO \text{ and } >C{=}O$$

3. Sulfonated products

$$\text{acid} + \text{conc. } H_2SO_4 \longrightarrow \text{acid} + PCl_5 \longrightarrow \text{acid chlorides} + Na_2SO_3 \longrightarrow \text{sulfonic acids}$$

4. Alcohols

$$\text{acid} + H_2 \xrightarrow[100\text{-}250 \text{ atm.}]{300\text{-}400^\circ} \text{85 per cent alcohols}$$

$$\text{acid} + CO \longrightarrow \text{alcohol}$$

5. Amines

$$\text{ketones} + H_2 + NH_3 \longrightarrow \text{90 per cent amines}$$

Uses.--

1. Soaps, dispersing agents, melting agents, emulsion breakers, emulsifiers.
   Salts, sulfonated acids, sulfonated alcohols.

2. Preservatives, driers, pigments.
   Salts.

3. Resins.
   Polyesters, vulcanized acids.

4. Plasticizers.
   Esters.

5. Fungicides.
   Esters and amines.

6. Soporifics.
   Barbiturates.

7. Perfumes.
   Isobutyl ester.

8. Miscellaneous.
   (a) Lubricating greases; (b) reclamation of rubber; (c) solvent for castor oil - mineral oil; (d) catalysts; (e) metallurgy.

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Patents:

U.S.	B.P.	F.P.
2,099,909	359,116	751,641
2,114,717	433,206	711,952
1,989,325	459,791	777,750
	445,223	780,208
		693,620
		669,517

Reported by H. Fineberg
May 15, 1940.

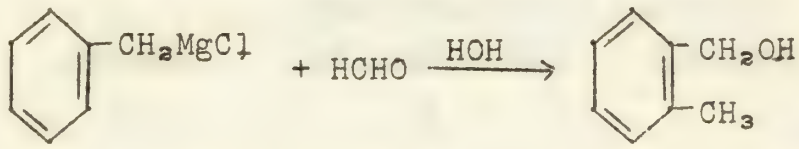
ABNORMAL REACTIONS OF GRIGNARD REAGENTS.

THE ALLYLIC REARRANGEMENT.

Johnson-Cornell University-Ithaca, New York

Organomagnesium halides are very widely used in studies of the mechanisms of organic reactions and in the proof of structures of compounds. Such utility would be markedly curtailed by uncertainties concerning rearrangements of the Grignard reagents.

The first reported rearrangement of this kind was observed in the following reaction:



Subsequent studies showed that rearrangements also occur in certain reactions involving α-$C_{10}H_7CH_2MgCl$ and $C_6H_5CH{=}CHCH_2MgCl$. All compounds showing this behavior have the grouping

$$H\text{-}\overset{\gamma}{C}{=}\overset{\beta}{C}\text{-}\overset{\alpha}{C}H_2MgX$$

The rearrangements result in the introduction of the entering group in the γ-position instead of the α-position, and a migration of hydrogen in the reverse direction, from the γ-position to the α-position.

Austin and Johnson reviewed the cases involving benzylmagnesium chloride. These data are summarized in Table I. Nearly all of the reactants listed as abnormal lead to the production of <u>both</u> <u>o</u>-tolyl and benzyl derivatives.

Table I

Reactions of Benzylmagnesium Chloride

Abnormal	Normal
Formaldehyde	Paraldehyde
Benzaldehyde	Alkyl and aryl ketones
<u>p</u>-Methoxybenzaldehyde	Acetals and ethyl orthoformate
Ethylene oxide	Ethyl acetate, benzoate and
Alkyl chloromethyl ethers	Carbon dioxide [carbonate]
Ethyl and methyl chlorocarbonate	Epichlorohydrin and chloro-
Ethyl formate	Allyl iodide [acetone]
Acetyl and benzoyl chloride	Mercuric chloride
Acetic and chloroacetic anhydride	Phenyl isocyanate
	Alkyl <u>p</u>-toluene sulfonates

The above data apply only to benzylmagnesium chloride. For example, it has been shown that the reaction between cinnamyl chloride, magnesium and carbon dioxide gives rise to a product of

rearrangement. That the rearrangement (abnormal reaction) depends on the nature of the reactant and the organomagnesium halide becomes apparent from an inspection of Table II.

Table II

Reactions of Benzyl- and ortho-Substituted Benzylmagnesium Chlorides

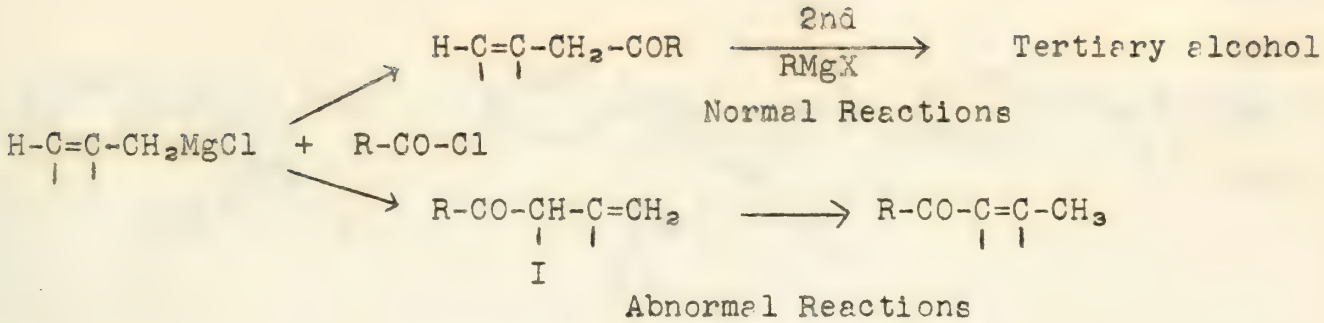
	Organomagnesium Chloride		
Reagent	Benzyl-	2-Chlorobenzyl	2,6-Dichlorobenzyl
CO_2	N	N	N
CH_3OCOCl	R	N	N
$(CH_3CO)_2O$	R	R	N
CH_3COCl	R	R	R

N = Normal
R = Rearrangement

From the standpoint of the reactants it appears that the tendency to produce rearrangements decreases in the order: acetyl chloride > acetic anhydride > methyl chlorocarbonate > carbon dioxide. In the Grignard reagents, the tendency to undergo rearrangement appears to decrease with the introduction of one ortho substituent and decreases further by the introduction of two ortho substituents. In the latter, the rearrangement necessarily leads to a p-tolyl derivative.

There is no doubt that an allylic rearrangement is taking place in the triad system. Indeed, Young and his coworkers have shown conclusively that the action of magnesium on cinnamyl chloride and related compounds gives rise to this phenomenon. Gilman has gone farther in showing that other metals such as zinc, cadmium, mercury and aluminum have a similar effect on benzyl chloride.

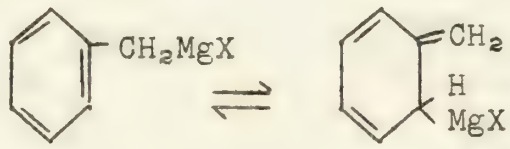
The addition of an acid chloride to the system $\overset{\gamma}{H-C}=\overset{\beta}{C}-\overset{\alpha}{CH_2}-MgX$ may be written, for example:



The abnormal reaction has been resolved into two steps, a point of view which is enhanced by the experimental evidence obtained by Prévost who showed that the action of Grignard reagents upon the halides of the type R-CH=CH-CH_2Br produced compounds corresponding in structure to the intermediate compound I. The intermediate may be isolated when the substituent on the γ-carbon atom does not activate the hydrogen sufficiently to cause it to migrate from the γ to the α carbon atom, i.e., the second step in the abnormal reaction. The second step is analogous to the keto-enol transformations. The effect of variations of R in the system RCH_2CO- is parallel to the effect in the system R-CHCH=CH_2; in both systems the activating effect of R-group diminishes in the order: acyl > phenyl > alkyl.

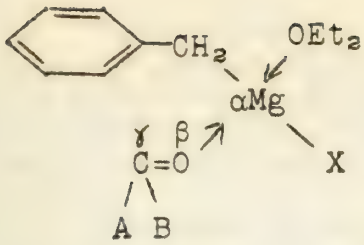
The effect of substituents in the triad system upon the first step of the rearrangement (α-γ migration of the entering group) is more obscure. In the system A-C=C-CH_2-B, the nature of the substituents A and B, as well as that of the reactant, have an important effect on the inherent tendency to undergo abnormal reaction.

Two principal theories have been advanced to explain the mechanism of the rearrangement. One of these involves the assumption of dynamic isomerism between the normal and an o-quinonoid form of the Grignard reagent:

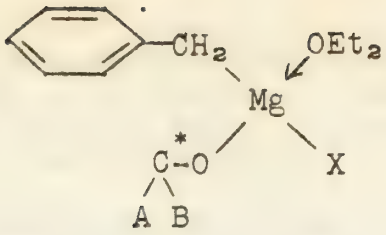


The other assumes that the change of structure occurs in the course of the reaction, through rearrangement of electrons in a free benzyl radical or ion. There are good reasons for rejecting both of these hypotheses.

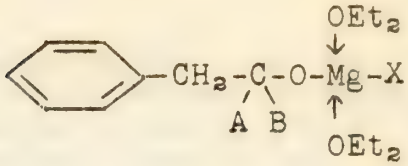
A more plausible explanation has been suggested by Johnson. The first stage of all Grignard reactions is the formation of a coordination compound. The subsequent transformations can be illustrated by the reaction between benzylmagnesium chloride and a reactant containing a carbonyl group, A-CO-B, giving rise to the coordination compound II.



II



III

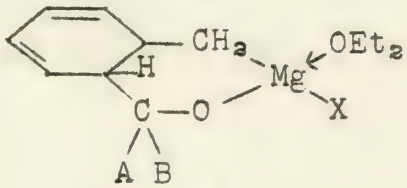


IV

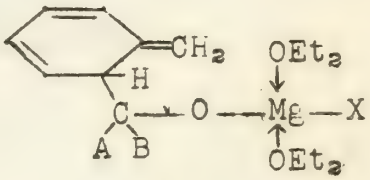
Both normal and abnormal reactions arise from a γ-α shift of electrons in the triad system C=O→Mg which would tend to leave the carbon atom γ with a sextet of electrons (C* in III). In the normal reaction the γ-α shift of electrons is completed by an α→γ migration of the benzyl group with its electrons (essentially as an anion); there is no rearrangement within the benzyl group. The octet of the magnesium atom is completed simultaneously by coordination with ether to give a stable normal product IV.

The abnormal reaction arises from a combination of several factors: (1) the presence of an allylic system (α', β', γ') in the organic radical of the Grignard reagent, (2) the proximity of the γ-atom of the triad system Mg ← O=C and the terminal atom of the allylic system present in the benzyl group, (3) the nature of the substituents A and B attached to the carbonyl group. In the allylic system of the organic radical, an α'→γ' shift of electrons makes possible an intramolecular chelation with the production of an ephemeral ring structure V. The electronic shift is completed by rupture of the linkage between the magnesium atom and the α'-atom of the allylic system (and coordination of the magnesium with ether) giving the product (VI).

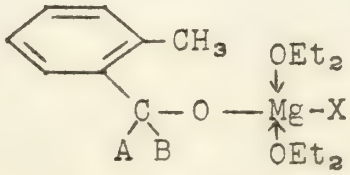
III →



V



VI



VII

This process is the first step of the rearrangement. In the case of simple allylic systems the reaction may not proceed farther, but with the benzyl group, a migration of hydrogen converts the o-quinonoid system into an o-tolyl group. The second step of the rearrangement has already been discussed.

The main points of the hypothesis may be summarized as follows: (1) formation of a primary addition product containing coordinate linkages; (2) transformation of the latter into a more stable system (a) by α,γ-rearrangement or (b) by chelation and subsequent ring opening.

This is an improved mechanism since it offers a definite criterion for explaining or predicting the behavior of a given reactant. Moreover it is operative in other important cases. Carothers has applied it to explain the formation of orthoprenes by the action of Grignard reagents on chloro-4-butadiene-1,2. It may be offered as a possible mechanism for a variety of reactions which are currently explained by hypotheses which are not wholly adequate. Among these are the C-alkylation of metallic derivatives of enols and related reactions (the Reimer-Tiemann reaction, the Kolbe synthesis, etc.).

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Reported by A. I. Rachlin
May 22, 1940.

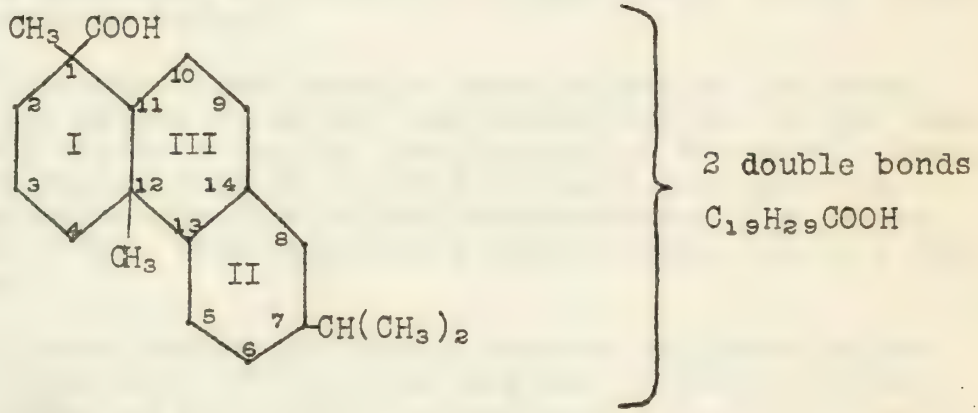
ABIETIC ACID

Ruzicka -- Hochschüle, Zurich

Abietic acid is the principle constituent of a commercial product obtained from rosin. Its esters are used as plasticizers for nitrocellulose products. Its salts, particularly those of manganese and cobalt, are used as driers in varnishes. It is also a plentiful source of phenanthrene derivatives.

Although Ruzicka has obtained a 90 per cent yield of abietic acid by distillation of rosin under low pressure, this method is not used ordinarily in its preparation. Instead, the original acids present in the rosin are isomerized to abietic acid by boiling a rosin solution in 98 per cent acetic acid for two hours and the crude acid which separates on cooling is recrystallized from dilute acetic acid. A 40 per cent yield of the acid known as "Steele's acid" is obtained by this method.

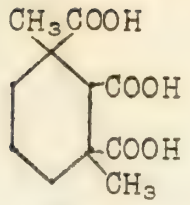
Since 1922, Ruzicka has been engaged in the determination of the structure of abietic acid. In spite of widespread investigations, the carbon skeleton was not determined completely until 1932.



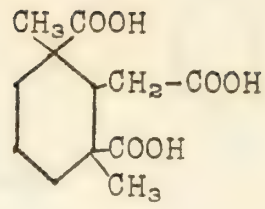
I

The presence of a hydrophenanthrene nucleus was shown in 1903 when abietic acid was dehydrogenated to yield retene ($C_{18}H_{18}$). The structure of retene was determined as 1-methyl-7-isopropyl phenanthrene. The carboxyl was located on C_1 by reduction to the hydrocarbon which was dehydrogenated again to retene; while if the carboxyl was reduced to the carbinol, dehydrated and dehydrogenated, it yielded homo-retene, a compound shown to be 1-ethyl-7-isopropyl phenanthrene.

The angular methyl group was located on C_{12} by Ruzicka who isolated the following acids from oxidation products of abietic acid.



II $C_{11}H_{16}O_6$



III $C_{12}H_{18}O_6$

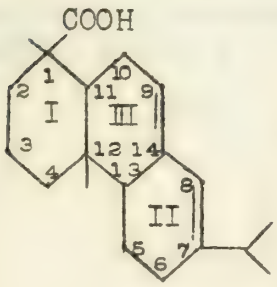
The dehydrogenation of II gave m-xylene while III yielded 1,2,3-trimethyl benzene. This indicates that the methyl groups are 1,3 with respect to each other and, hence, the angular methyl group is on C_{12}.

Two double bonds were indicated by analyses, benzoyl peroxide titrations and the formation of dichlorodihydroabietic acid and dibromodihydroabietic acid by treatment with anhydrous hydrochloric or hydrobromic acid.

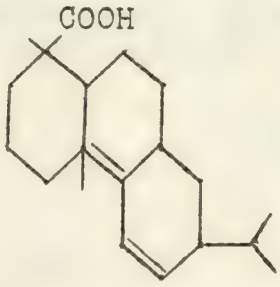
Since 1932, most of Ruzicka's work has been an attempt to locate the two double bonds. The isolation of acids II and III, above, indicated that ring I withstood oxidation and, hence, does not contain any double bonds.

By comparison with known sterols, spectrographic evidence indicated that the double bonds are conjugated but not in the same ring. Additional evidence for the conjugation of the double bonds was presented by Fieser when he coupled the acid with p-nitrobenzenediazonium chloride and 2,4-dinitrobenzenediazonium chloride, a reaction which occurs with conjugated double bonds, but not with isolated systems.

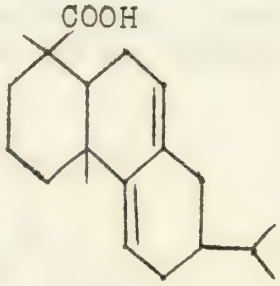
Ozonization experiments yielded no acetone or formaldehyde, indicating that exocyclic double bonds are not present. On the basis of this evidence five possible structures for abietic acid remain (IV through VIII).



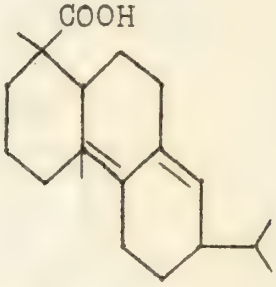
IV



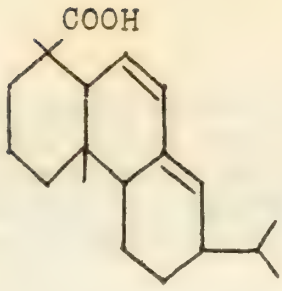
V



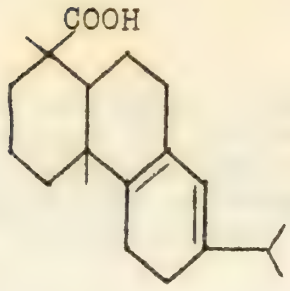
VI



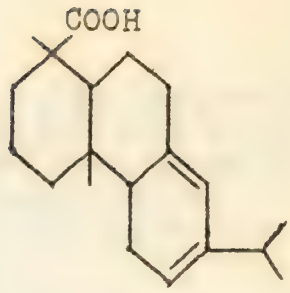
VII



VIII



IX



X

The structure of *l*-pimaric acid, which may be obtained from rosin and isomerized into abietic acid by the mild treatment described for the preparation of abietic acid, has been shown definitely to be either IX or X. Structure IV could be produced more easily by double bond shift than any other.

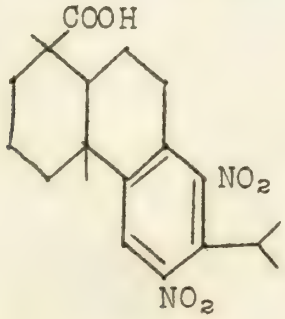
Numerous investigators have reported the formation of isobutyric acid by oxidation and ozonization experiments. Ruzicka has recently shown that dehydrogenation of tetrahydroxyabietic acid and dihydroxy abietic acid, prepared by careful oxidation of abietic acid with $KMnO_4$, yields a mixture of 1-methyl phenanthrenol-7 and retene. This is conclusive proof that a double bond is on C_7.

The acid III, above, has been isolated by other investigators, and is evidence for a double bond on C_9.

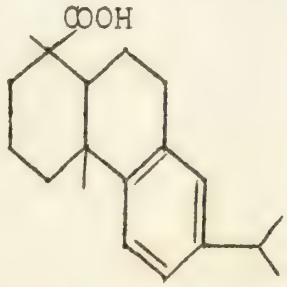
Although most of the evidence given here is indicative, not conclusive, Ruzicka announces that he will show definitely in a later publication that formula IV represents the true structure of abietic acid.

<u>Some Reactions of Abietic Acid</u>.--Many different reactions with, and on abietic acid have been attempted; most of them give rise to amorphous products which generally cannot be identified. Many of these reactions are patented.

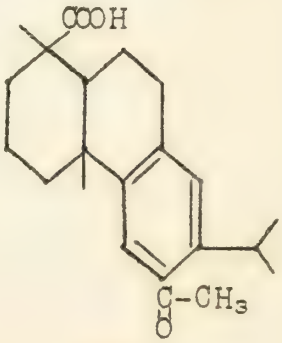
Abietic acid, when heated to about 300°, yields a mixture called "pyroabietic acid." Nitration of this product with mixed acids gives a dinitro compound shown to be compound XI.



XI



XII



XIII

If pyroabietic acid is sulfonated, a sulfonic acid derivative is formed, which can be hydrolyzed to produce a 40 per cent yield of dehydroabietic acid (XII). Pyroabietic acid has been shown to be a mixture of dehydro-, dihydro- and tetrahydroabietic acids. The acetyl derivative (XIII) is formed with acetyl chloride and $AlCl_3$.

The esters of abietic acid may be formed and there are many commercial methods for doing this. The best laboratory method is by the use of diazomethane. The esters may be reduced to abietinol.

Abietic acid may be reduced easily by platinum catalyst at low pressures in a variety of solvents to yield a dihydroabietic acid, but only with difficulty is the tetrahydro acid produced.

It yields, on oxidation, a variety of products depending upon the strength and quantity of the oxidizing agent used. Thus, selenium dioxide yields 6-hydroxyabietic acid. Potassium permanganate yields various products discussed before. Nitric acid will produce the C_{11} and C_{12} acids (II and III) in poor yields. Lead tetraacetate and permonophthalic acid may be used for partial degradation.

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Reported by F. J. Wolf
May 22, 1940.

SUBSTITUTION

The term substitution, in its widest sense, refers to any process in which one atom or group is displaced by another. This concept arose early in the history of organic chemistry and such men as Dumas (1834) and Gerhardt (1839) proposed theories to account for and predict the course of substitution reactions. The subject has intrigued investigators ever since and although numerous theories have been advanced, they are still quite inadequate in explaining the true nature of the process.

It is interesting that some of the simplest reactions of organic chemistry are the most difficult to explain. Much of the work on substitution has been done in the aromatic series. This is probably due to the greater ease with which the reactions can be controlled and studied. The theories of aliphatic substitution are, as a result, somewhat limited.

Walden's discovery that certain substitution reactions in optically active compounds led to an inversion in rotation upset the simple idea of a direct atom for atom exchange. Some twenty odd theories have been developed to attempt to explain why a substituent does not take the place of the atom or group it is replacing and to predict what place a substituent will occupy under certain definite conditions. Within the last few years, Meer and Polanyi and Ingold and Hughes have presented theories which will predict, at least in some cases, whether or not a Walden inversion will take place.

In order to present a clear picture of the mechanism of substitution, attempts have been made to find a general scheme which might be applicable to all cases. It has been assumed that addition must first take place; this is followed by elimination. This conception appears possible in aromatic compounds, but is much less likely to occur with the saturated aliphatic hydrocarbons. Erroneous assumptions must be made to account for an intermediate complex formation.

Meisenheimer (1927) gave a physical picture of the Walden inversion which depended upon the direction in which the new substituent approached the asymmetric atom. This idea presented substitution as a bimolecular reaction, but still told nothing about its mechanism. Ingold considered the Walden inversion to be a stepwise reaction and advanced two types of substitution:

Type I: $R\text{-}X \rightleftharpoons R + X;\ R + Y = RY$

Type II: $Y + R\text{-}X \rightleftharpoons Y\text{-}R + X$

In type I a decomposition into ions takes place; type II differs from earlier hypotheses in that it does not assume the formation of a loose intermediate addition compound, Y····R-X. The two

types of substitution are demonstrated by the alkaline hydrolysis of methyl iodide.

Type I (monomolecular)

$$CH_3I \underset{}{\overset{slow}{\rightleftharpoons}} CH_3^+ + I^-;\ CH_3^+ + OH^- \overset{rapid}{\rightleftharpoons} CH_3OH$$

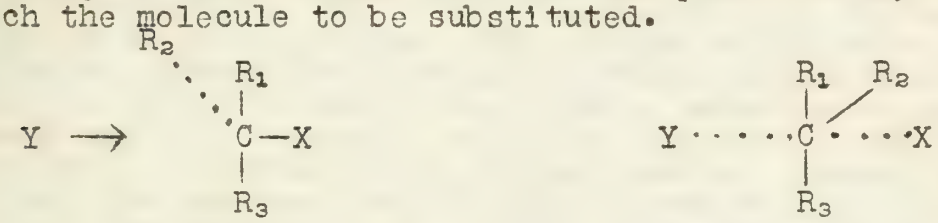
Type II (bimolecular)

$$CH_3I + OH^- = CH_3OH + I^-$$

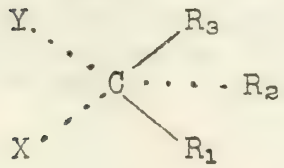
The steric nature of substitution is considered to be of two types. Meer and Polanyi have developed a "negative mechanism" of substitution; that is, a negative substituent is exchanged by a negative ion.

$$RBr + Cl^- = RCl + Br^-$$

They assume that the nature of the substituent and the manner of its approach are the factors which determine whether or not a configurational change will take place. As a consequence, it is claimed that substitution by negative ions is necessarily connected with configurational inversion. The theory of Ingold and Hughes is concerned mainly with the type of substitution. Substitution is looked upon as a continuous process; as one atom or group (Y) approaches, the other (X) recedes. There is at no time a rupture of a strong chemical bond or the formation of a new one. According to these ideas there are two possible ways for Y to approach the molecule to be substituted.



(I)



(II)

Theoretical considerations show that reaction I requires less energy than reaction II. Therefore, reaction I will take place more rapidly than II and bimolecular substitution, in general, leads to a change in configuration.

Ingold has developed what he considers to be a general mechanism for all substitution reactions. This is divided into two types or classes of reactions described as "electrophilic" and "nucleophilic." The processes may be represented by the following general equations where the dotted lines indicate the fate of the electron pairs originally forming the covalent bonds

which are broken:

Electrophilic substitution

$$\begin{cases} R-\vdots X + Y-Z = R-Z + X-Y \\ R-\vdots X + Z \quad = R-Z + X \end{cases}$$

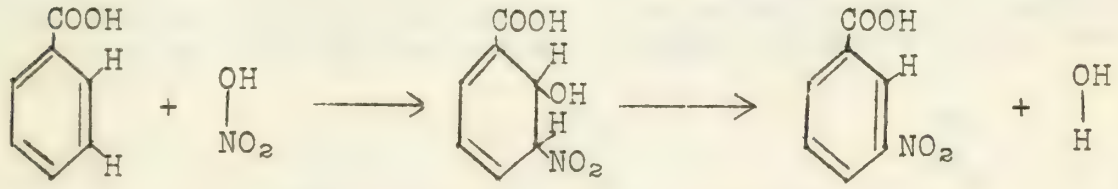
Nucleophilic substitution

$$\begin{cases} R\vdots-X + Y-Z = R-Z + X-Y \\ R\vdots-X + Z \quad = R-Z + X \end{cases}$$

It is important to realize that the terms "electrophilic" and "nucleophilic" have no reference to the electrical condition of the reagent, but exclusively to its electron-accepting or electron-donating capacity.

The theoretical attempts to classify aromatic substitution started with Kekulé's ring formula for benzene in 1865 and were aided by Körner's work on the orientation of benzene derivatives. At an early date it became evident that the main factor determining the position of substitution was the nature of the group or groups already present. Attempts to express this fact in a generalized form led to various orientation rules.

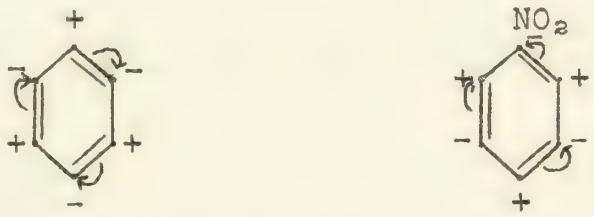
Substitution can, theoretically, occur at every point in an aromatic substance, and it is even possible to replace substituent groups other than hydrogen, but, except in the case of symmetrical substances, substitution usually proceeds at rates which differ widely in different positions. Hence, substituent groups already present within an aromatic molecule must act by modifying the velocity of substitution at distant points. Obermiller pointed out that one can consider an initial weakening of the carbon to hydrogen covalent bond, by induced influences, to be an essential stage in any substitution reaction. Holleman suggested that aromatic substitution involved the initial addition of two groups to an unsaturated linkage of the aromatic ring, followed by the elimination of a simple inorganic molecule such as water or a hydrogen halide.



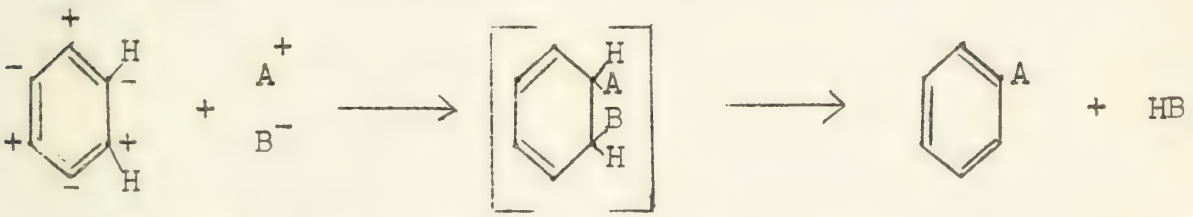
This simple addition-elimination mechanism was accepted for a number of years.

The electronic theories of aromatic substitution, which today seem more logical, arose as early as 1911 when Fry suggested that positive and negative charges actually reside upon the atoms constituting the aromatic molecule. In 1920 Lapworth applied his earliest theories of polarity and chemical change to the case of aromatic substitution, and explained the production of reactivity at particular points in a benzene ring by a theory of induced electrical polarity. According to Lapworth there can be transmitted within any aromatic ring, at the moment of reaction though not necessarily in the compound before activation, an electrical polarization. The presence of a key atom of definite polar character was necessary in a directing group before this transmission of electrical polarity took place preferentially in any one specific way. Lapworth's views have since been expanded and amplified by Robinson, Ingold, and others, but no real new ideas have been introduced.

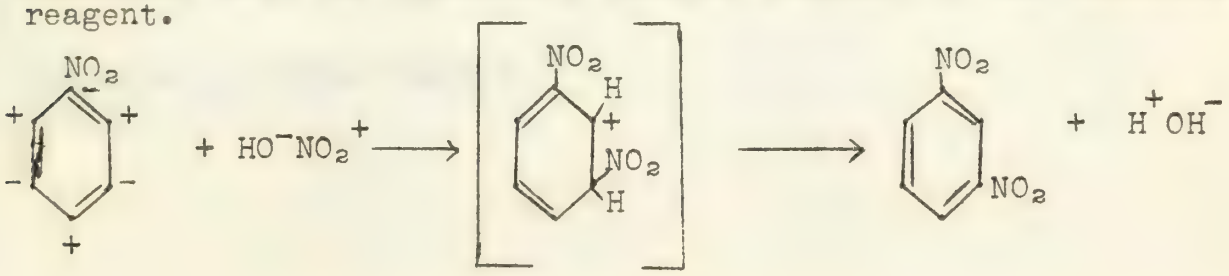
It is assumed that the aromatic compound is polarized first by the presence of either internal or external influences. For example:



The substituting group may then enter the molecule by one of two mechanisms. The reagent (AB) is likewise polarized so that an addition might take place as follows:



Recent work by Price and others seems to indicate that the primary addition consists only in the attachment of a cationoid group to an atom carrying a high degree of negative affinity. This then is followed by the expulsion of a proton which is neutralized by combining with the oppositely charged fragment of the reacting reagent.



Although the theories of substitution become more numerous as time goes on, a general solution to the problem is still lacking. Probably no such mechanism will ever be found since it seems difficult to imagine that such a wide variety of reactions must take place in the same manner.

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Reported by Norman Rabjohn
May 22, 1940.

CONFIGURATION OF GLYCOLS FROM THE BIMOLECULAR REDUCTION OF ALDEHYDES

Sörensen, Steve, and Samuelsen - Tech. Hochschule in Trondheim

The bimolecular reduction of aldehydes and ketones to glycols and pinacols respectively may give rise to both meso and racemic forms. The separation of the glycol into two forms is a tedious and difficult task and has been successful in but a few cases.

Glyoxylic Acid.--The zinc-copper couple reduction of glyoxylic acid gives only the racemic tartaric acid.

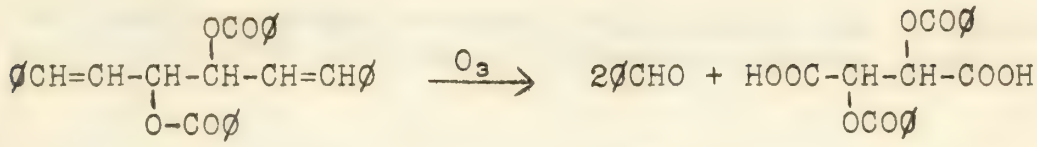
Acrolein.--Kuhn and Rebel reduced acrolein with the zinc-copper couple and obtained only the meso form of divinyl glycol. They proved its configuration by ozonization to mesotartaric acid. Lespieau and Wiemann, however, were able to separate the glycol into two forms, a solid melting at 18° and the other a liquid. The solid form gives allodulcitol exclusively by oxidation with $AgClO_3$-OsO_4 and must, therefore, be mesodivinyl glycol. Oxidation of the mixture of glycols gives both dl-mannitol and allodulcitol. Therefore, both racemic and meso forms are present but the relative amount of each is uncertain.

Crotonaldehyde.--The reduction of crotonaldehyde with the zinc-copper couple gives a glycol which was separated into the meso form, m.p. 48°, and the racemic form, m.p. 28°. The separation was brought about by Wiemann who fractionally crystallized the phenylurethane derivatives. Young and coworkers reduced the dipropenyl glycol with platinum and were able to separate the dipropyl glycol into a meso and racemic form. Phase relationships existing between the two dipropenyl glycols and also their 3,5-dinitrobenzoate derivatives indicate that the two forms are produced in equal amounts.

Benzaldehyde.--The final configuration of the glycol produced by the bimolecular reduction of benzaldehyde depends chiefly upon the reducing agent used. Two forms have been isolated and their configuration proved but little information is available concerning the relative amounts of each. A yield of 75% of the meso form was reported when zinc and hydrochloric acid were used as the reducing agent, whereas both racemic and meso forms were found when sodium and alcohol or vanadous salts were used. However, the ratio in which the two isomers are produced has not been established.

Cinnamic Aldehyde.--Sörensen, Steve and Samuelsen have reduced cinnamic aldehyde with the zinc-copper couple. The mesohydrocinnamoin was isolated in a 20% yield. Benzoylation of the mother liquor with benzoyl chloride in pyridine solution at 0° gave a crystalline dibenzoate of m.p. 165°. A mixed melting point with pure mesodibenzoylhydrocinnamoin (m.p. 173-174°) showed a depression of 30-40°. The constitution of the racemic dibenzoylhydro-

cinnamoin was proved by ozonization to racemic dibenzoyl tartaric acid and benzaldehyde.



The racemic compound was isolated in a 20-21% yield. Therefore, the racemic and meso forms are produced in equal amounts. Saponification of the racemic dibenzoylhydrocinnamoin to racemic hydrocinnamoin gave a crystalline product m.p. 107.5°. Rebenzoylation gave the dibenzoate of m.p. 165° which indicates that no change in configuration occurs upon saponification.

Acetophenone.--Acetophenone has been reduced electrolytically yielding both the racemic and meso forms. Many other cases of bimolecular reduction have been reported but the resulting glycol has either not been separated or the configuration of the glycol proved.

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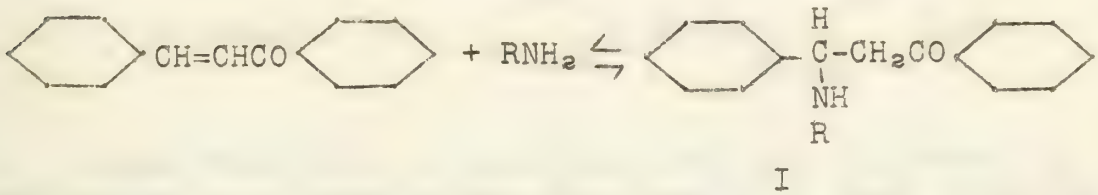
Reported by R. W. Upson

THE ADDITION OF METHOXYLAMINE TO UNSATURATED KETONES

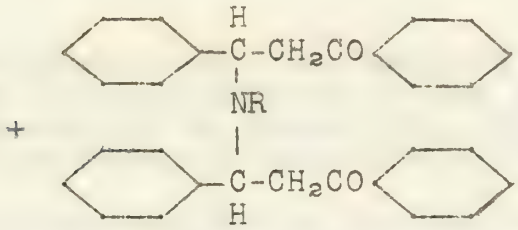
A. H. Blatt -- Howard University

Many basic nitrogen compounds will add to the 1,4-positions of such α,β-unsaturated ketones as benzalacetophenone (equation 1).



(1)

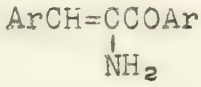
I



R = OCH_3

II

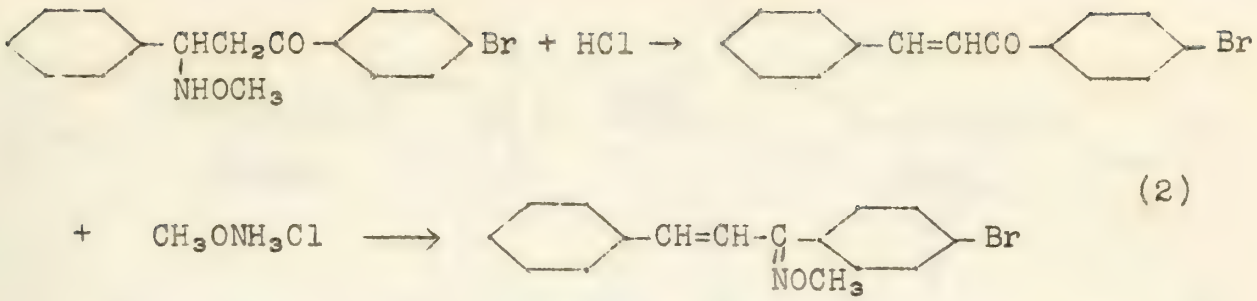
The paper that is reported here deals with the reversible addition of methoxylamine, and the rearrangement of the addition compounds of type I to α,β-unsaturated-α-amino ketones of type III.



III

The addition of methoxylamine takes place without the addition of any catalyst. In fact if a strong base is added the reaction will not stop with the addition compound, but will immediately rearrange to the aminoketone.

The reversibility of the reaction is shown by the behavior of the addition product on heating <u>in vacuo</u> or in the presence of a methoxylamine acceptor. These compounds may be distilled unchanged in a high vacuum (1 to 2 mm.), but if they are distilled in a moderate vacuum (75 mm.) they give the unsaturated ketone and methoxylamine. Upon heating an alcoholic solution of the addition product with benzaldehyde the reaction is reversed and the free base reacts with the aldehyde. When the salt formed by the addition product with an halogen acid is heated in alcoholic solution the oxime methyl ether of the unsaturated ketone (IV), as well as the ketone itself, is obtained (equation 2).

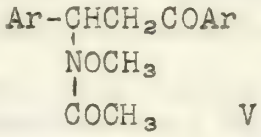


(2)

These facts are in accordance with the discovery that while methoxylamine hydrochloride adds readily to both aldehydes and ketones, the free base adds only to aldehydes and the most reactive ketones.

Since the primary addition compound is a weak base it can undergo addition to a second molecule of the unsaturated ketone to form a compound represented by formula II. The cases of the formation of these <u>bis</u> compounds are indicated in Table I.

The acetyl derivatives of the addition compounds (type V), also regenerate the unsaturated ketone on heating. However, on treatment with alkali they do not rearrange to an aminoketone, but produce the original ketone.

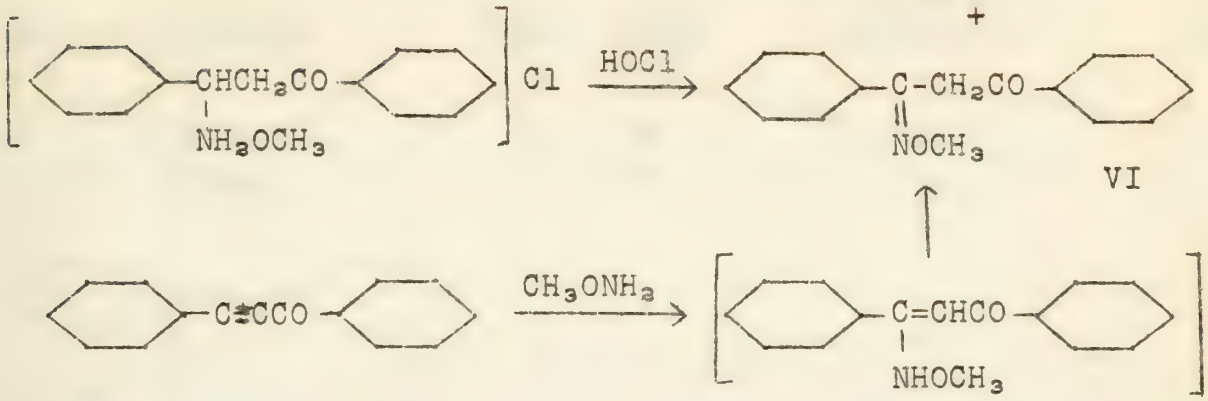


V

Although a great deal is known about 1,4-addition to α,β-unsaturated ketones, and it was quite certain that equation 1 represented the course of the reaction, definite evidence for the structures assigned was needed, in view of the subsequent rearrangements.

This evidence was obtained by oxidation of I to the monooxime methyl ether of dibenzoyl methane (VI). The structure of VI was established by two independent syntheses. These reactions are schematically represented by the following equations:

+



The most interesting property of the addition compounds is their ability to rearrange to α,β-unsaturated-α-aminoketones when under the influence of strong base (equation 3)

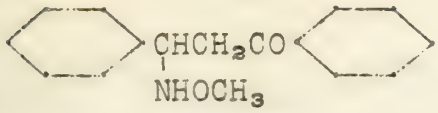
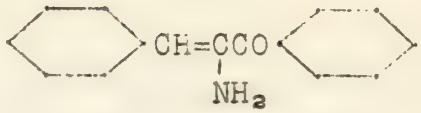
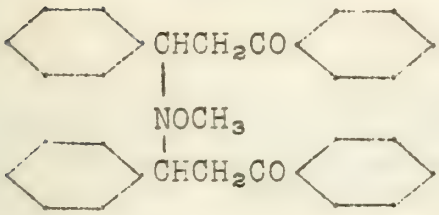
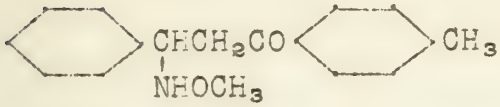
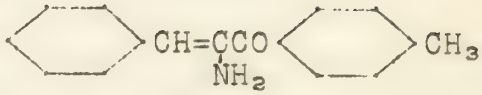
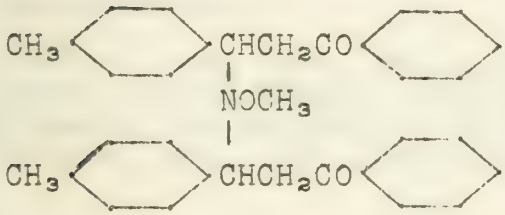
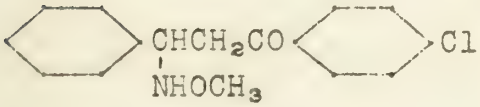
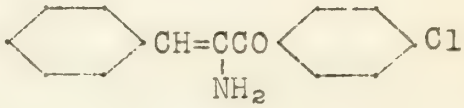
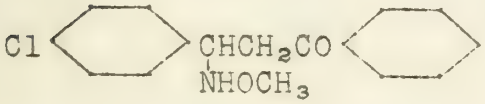
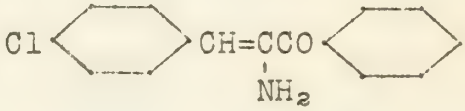
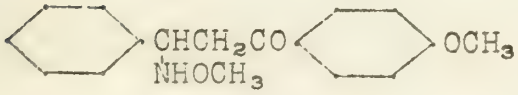
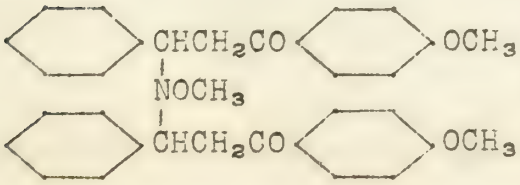
$$\mathrm{ArC(H)(NHOCH_3)-CH_2CO} \xrightarrow{\mathrm{NaOCH_3}} \mathrm{ArCH{=}C(NH_2)-COAr} + \mathrm{CH_3OH} \qquad (3)$$

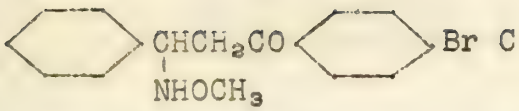
The reaction is important for it seems to be general, the yields are good (Table I), and it makes a little known, but interesting class of compounds readily available.

No mechanism for the rearrangement was proposed. The author stated that more experimental work was needed to decide between several possible courses the reaction might take.

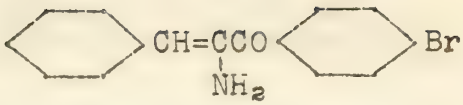
α-Aminobenzalacetophenone had been obtained by Dufraisse and Moureu on treating α-bromobenzalacetophenone with ammonia. They proved the structure of this compound by acid hydrolysis to phenylbenzylglyoxal. Earlier Ruhemann and Watson had prepared a compound from benzylidene dibromide and ammonia that they believed to be the β-aminobenzalacetophenone. Dufraisse and Moureu showed that Watson's compound really was the α-isomer. Wieland also prepared a substance by the action of ammonia on p-nitrobenzylidene dibromide. Very likely this compound is another member of the same series.

TABLE

Addition Product	Temp.*	Yield	Rearrangement Product	Yield
	H C	78 64		94
	C	--		
	C	60		64
	C	--		
	C	70		66
	H	86		80
	H	65		
	C	--		



C 83



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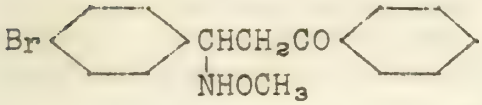
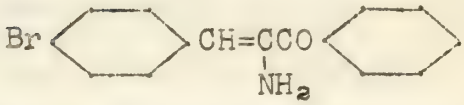


H 63



90

* H = hot C = cold

In summary: This paper reports the reversible addition of methoxylamine to α,β-unsaturated ketones, the proof of the structure of the addition products, and the rearrangement of the addition products to α-aminoketones.

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Wieland, Ber., 37, 1150 (1904).

Reported by Carleton A. Sperati

ARYL PYRIDINES

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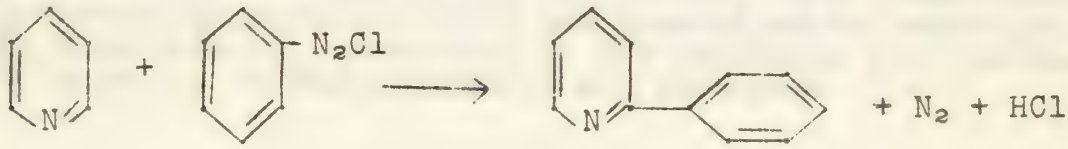
E. E. Butterworth -- The University of Manchester

Many attempts at the synthesis of aryl pyridines by the action of a diazonium salt upon pyridine are recorded in the literature. In all cases, however, the yields were small (1-18%) thus making the method impractical for the preparation of these compounds.

Other methods for the preparation of phenyl pyridines not involving the use of diazonium salts have also been described, but again yields are often very poor. Improved methods have been introduced recently using phenyl lithium or phenyl magnesium bromide, but these reactions cannot be regarded as general since they would be inapplicable to the preparation of many substituted phenyl pyridines.

A new and simple general method is now described for the preparation of aryl and substituted aryl pyridines. The procedure consists in the slow addition of an aqueous solution of a diazonium salt to an excess of pyridine at 20-70° and yields of 20-80% are obtained depending upon the amine used. The reaction is as follows:

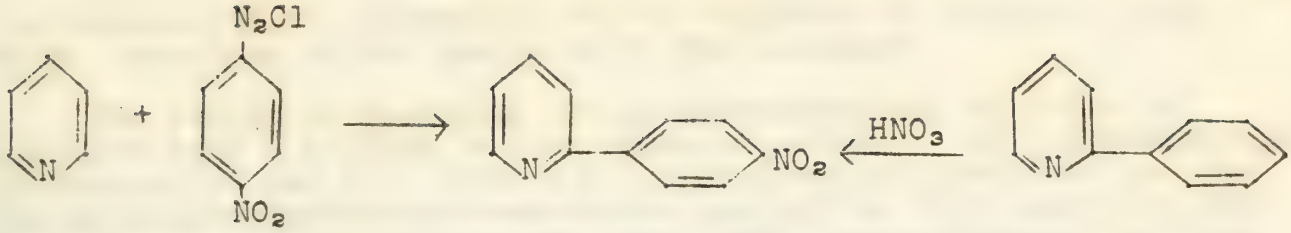


I

If, on the other hand, pyridine is added to the diazonium salt, a point is reached at which a vigorous reaction sets in, which in many cases cannot be controlled and the formation of much tar results. The product normally consists of the 2-, 3-, and 4-isomers which can be easily separated.

Addition of an aqueous solution of benzene diazonium chloride to an excess of pyridine at 30° gave a 40% yield of a mixture of 2-, 3-, and 4-phenylpyridines. Separation of the isomers by fractional crystallization of the picrates showed that 2-phenylpyridine (I) predominated.

By addition of aqueous solution of p-nitrodiazonium chloride to an excess of pyridine at 40° gave a mixture of crude p-nitrophenylpyridines in 75% yield. Separation by the fractional crystallization of the picrates showed the mixture to be predominately 2-p-nitrophenylpyridine (II).

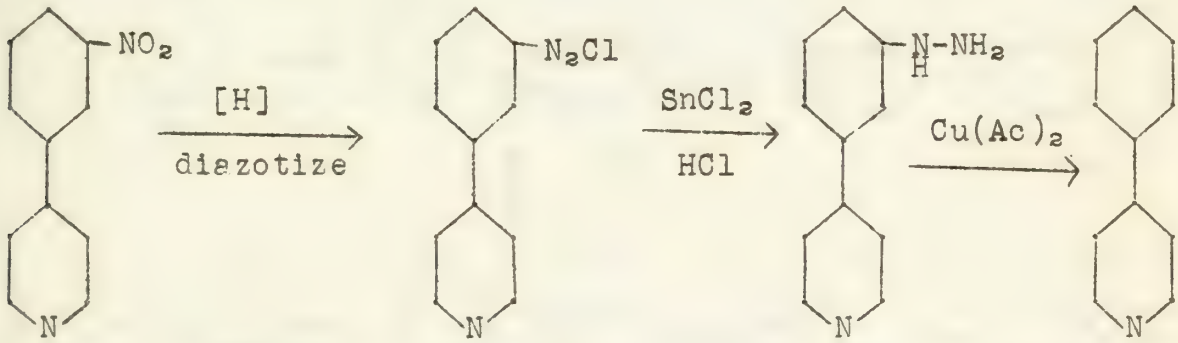


II Also 3- and 4-isomers

Similar reactions were carried out with diazotized m-nitroaniline and o-nitroaniline obtaining the corresponding nitrophenylpyridines in about 35% yield.

The constitution of the nitrophenylpyridines depends upon the use of 2-, 3-, and 4-phenylpyridines as reference compounds. Their constitution has been placed beyond doubt since they form characteristic picrates, and on oxidation the phenyl group is oxidized to yield the corresponding pyridine carboxylic acid.

The three p-nitrophenylpyridines obtained from p-nitroaniline were identified by correspondence with the previously described compounds, which were made by the nitration of the phenylpyridine as shown above. In the case of the m-nitrophenylpyridines the 2-m-nitrophenylpyridine was identified by correspondence with the compound previously described in the literature. The constitution of the 4-m-nitrophenylpyridine (III) was identified by reduction, followed by diazotization, reduction to the hydrazine and treatment with copper acetate. 4-Phenylpyridine was produced.



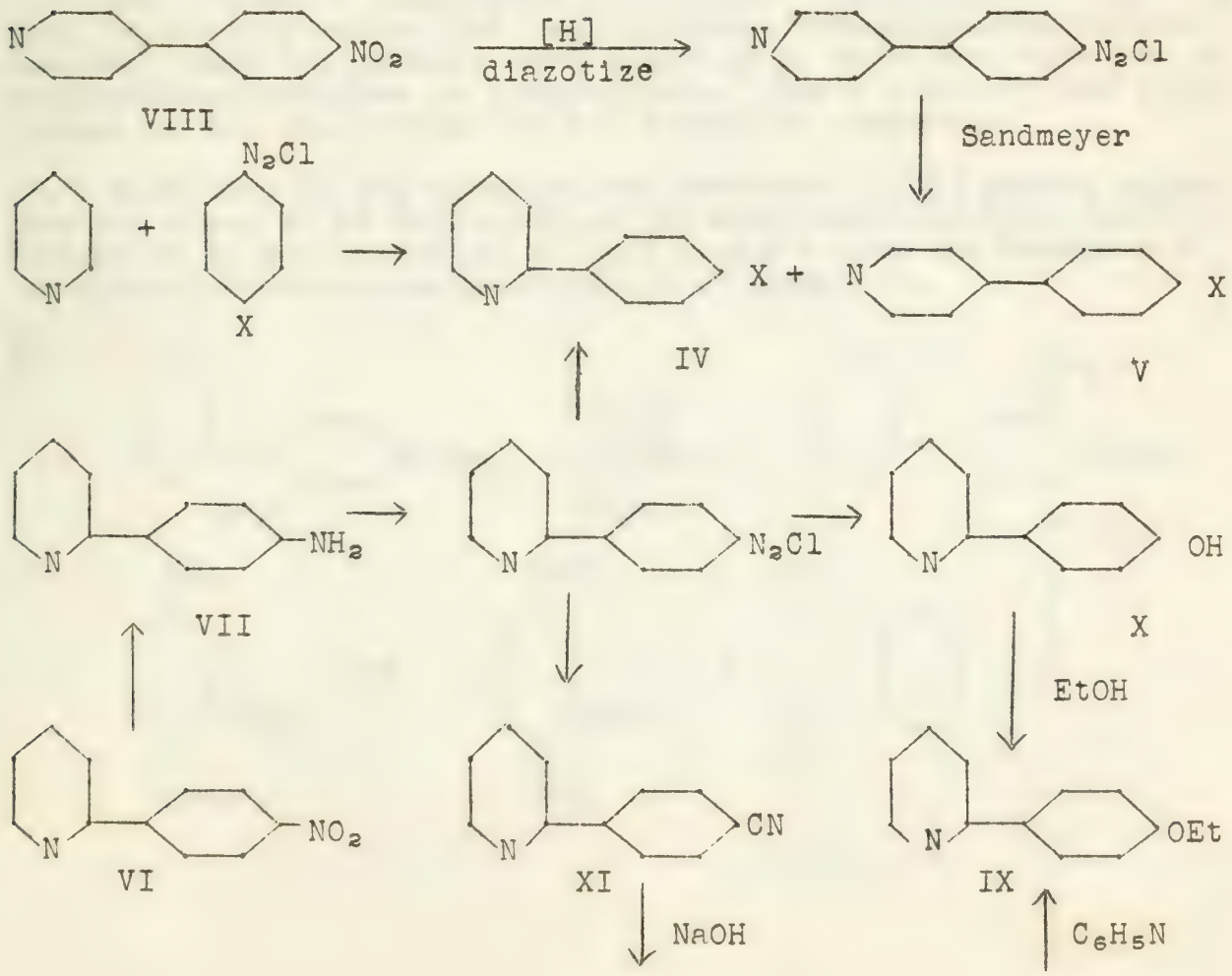
In the case of the o-nitrophenylpyridines the identity of 3-o-nitrophenylpyridine was proved by conversion to 3-phenylpyridine by the same method used above. The identity of 2-o-nitrophenylpyridine was proved by reduction diazotization and treatment with methyl alcohol to give 2-phenylpyridine, although this reaction was expected to yield the 2-o-methoxy compound instead. By elimination the third isomer, obtained only in small quantity must be the 4-o-nitrophenylpyridine.

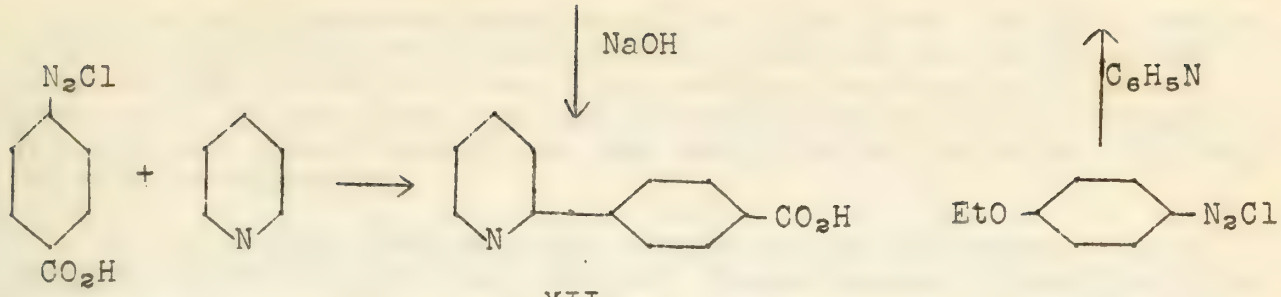
In general, it is the 2-isomer which predominates in these reactions. However, in the reaction of pyridine and diazotized

o-nitroaniline the proportion of the 3-isomer is unusually high with a decrease in the quantity of the 4-isomer.

The action of p-chloro- and p-bromodiazonium chloride on pyridine gave a mixture of two isomeric p-chloro- and p-bromophenylpyridines (IV and V). Both the 2-p-chlorophenylpyridines and the 2-p-bromophenylpyridines were characterized by their identity with the corresponding compounds prepared from 2-p-nitrophenylpyridine (VI) by reduction to the amino compound (VII) and conversion to the halogen compound by means of the Sandmeyer reaction.

Diazotized p-phenetidine and pyridine gave a mixture from which two isomers were isolated, one was identical with the compound (IX) prepared from 2-p-aminophenylpyridine (VII) and ethanol. 2-p-Aminophenylpyridine (VII) has also been converted by means of the Sandmeyer reaction into 2-p-hydroxyphenylpyridine (X), 2-p-iodophenylpyridine (IV) and 2-p-cyanophenylpyridine (XI). Hydrolysis of this last compound with 10% sodium hydroxide yielded the corresponding carboxylic acid (XII) which was converted to the methyl ester. It was also identical with the acid prepared by the action of diazotized p-aminobenzoic acid on pyridine. The last reaction was also shown to give rise to some 4-phenylpyridine 4'-carboxylic acid since decarboxylation of the crude product produced both 2- and 4-phenylpyridine.



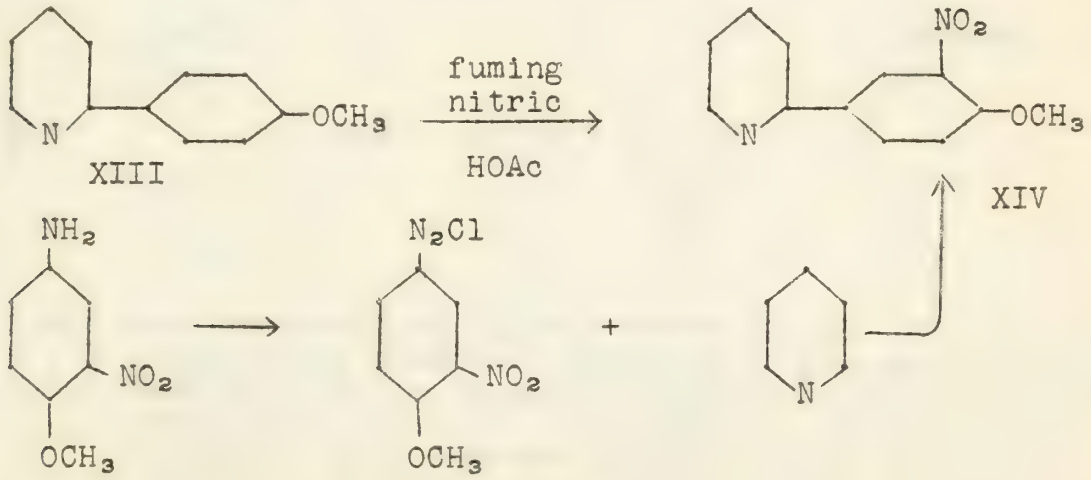


XII

The action of diazotized o-anisidine on pyridine gave a mixture of o-methoxyphenylpyridines in 50% yield and on fractional crystallization of the picrates yielded three isomeric products, the main portion of which proved to be 2-o-methoxyphenylpyridine by oxidation with acid permanganate to picolinic acid. The 3-p-methoxyphenylpyridine, was identified by its identity with the same compound prepared from 3-o-nitrophenylpyridine by reduction to the amine diazotization and reaction with methyl alcohol. This reaction is in sharp contrast to the reaction mentioned previously whereby the action of methyl alcohol on diazotized 2-o-aminophenylpyridine gave 2-phenylpyridine and not 2-o-methoxyphenylpyridine. No explanation is given for this fact.

The action of diazotized p-anisidine and m-anisidine gave the same reaction yielding the corresponding methoxyphenylpyridines. However, only two isomers were isolated in each case with the 2-methoxyphenylpyridine in predominance. Their identity was established in the same manner as the o-methoxy compounds.

Nitration of 2-p-methoxyphenylpyridine (XIII) gave a single product shown to be 2-3'-nitro-4'-methoxyphenylpyridine (XIV) as was shown by the isolation of this product from the reaction of diazotized 3-nitro-4-methoxyaniline on pyridine.

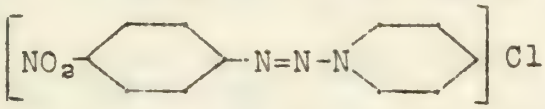


XIII

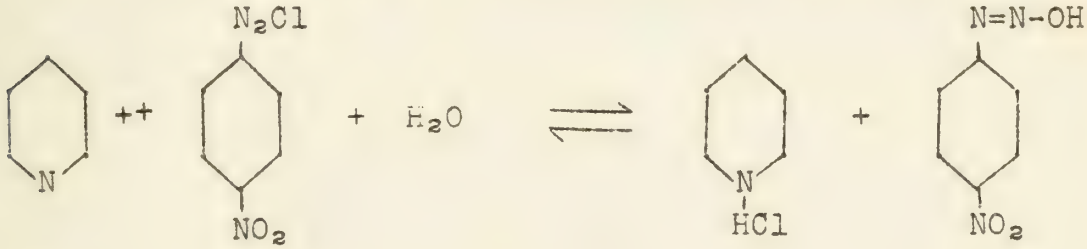
Nitration of 2-o-methoxyphenylpyridine also gave a single product, shown to be 2,5'-nitro-2'-methoxyphenylpyridine in the same way as above by the action of diazotized 4-nitro-2-methoxyaniline on pyridine. In the nitration the powerful o-p directing influence of the methoxyl group determines the position of the entering group as would be expected.

It is highly probable that in all reactions between the diazonium salts and pyridine that all three isomeric phenylpyridines are formed in each case although it was possible to isolate only two isomers in some cases. The 2-phenyl isomer was always present in greatest amount and the 3-phenyl isomer usually in the smallest amount. Failure to isolate one of the isomers in some of the reactions is attributed to practical difficulties and working with insufficient quantities.

With regard to the mechanism of this reaction the following observations were made. Addition of pyridine to aqueous p-nitrobenzene diazonium chloride gives no perceptible reaction until the base has been added somewhat in excess of that equivalent amount of acid (both free and combined) present, after which further addition of pyridine results in a vigorous reaction. Also if pyridine is added to aqueous p-nitrobenzene diazonium chloride equivalent to the amount of free acid present together with sufficient amount to form an intermediate compound of the type:



and the resulting mixture is stirred with an excess of benzene, p-nitrobiphenyl but no p-nitrophenylpyridine is formed. Since aqueous diazonium salts do not react with benzene, a reactive intermediate of the type indicated may be involved. Alternatively the active agent may be the diazohydroxide produced thus:



And in this case the reaction closely resembles that of the biaryl synthesis of Gomberg, by which dry diazonium salts and diazotates are coupled with an aromatic nucleus. Further aqueous diazonium salts do not react with solutions of quaternary pyridium salts to yield aryl pyridines. With aqueous pyridine methyl iodide, p-nitroaniline diazonium chloride gives only p-iodonitrobenzene, and with aqueous methyl methosulfate no action takes place at room temperature but on heating p-nitrophenol is formed.

It appears most likely that the active agent is a diazohydroxide and the underlying mechanism involves free radical formation as the union of a diazotate and an aromatic nucleus in the biaryl synthesis. The free radical mechanism is also favored by the fact, that in general all three isomeric aryl pyridines are formed. This indicates that the normal polar directive influences are not operating, either in any process of direct substitution or in any process involving a migration from the nitrogen atom.

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J. W. Haworth, I. M. Heilbron and D. H. Hey, J. Chem. Soc., 1940, 349, 359.
E. E. Butterworth, I. M. Heilbron and D. H. Hey, ibid., 1940, 355.
Forsyth and Pyman, ibid., 1926, 2912.
M. Gomberg and W. E. Bachmann, J. Am. Chem. Soc., 46, 2339 (1924); 48, 1372 (1926).
Greive and Hey, J. Chem. Soc., 1938, 108.
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Mohlau and Berger, ibid., 26, 1994 (1893).

Reported by C. F. Huber

REDUCTIONS WITH PLATINUM AND PALLADIUM CATALYSTS

Because of the versatility of various types of platinum and palladium catalysts, and the, in general, excellent yield that may be obtained through their use, it seemd worthwhile to list source material for a number of typical reductions which could be used as a guide in further research.

The table of reductions, all of which are carried out at easily attainable temperatures and pressures, has entries under Compound, Catalyst, Product and Yield. The compounds are listed under the functional group attacked. Since many of the reductions have been carried out with only one catalyst, the yields as listed are not necessarily the best which could be obtained. It will be noted that in some cases the type of catalyst has a marked effect upon the course of the reaction. A factor which is not listed in the table, but which is often of the greatest importance, is the solvent.[35] Striking examples of the various products obtained through the use of different solvents will be found in certain of the references.[43,76]

The poisonous action of many of the metals of the activity of the catalyst is also an important factor.[80,81,82] In certain reductions it is useful to add a poison so that the reduction will stop at the desired point. An example is the use of quinoline and sulfur in the reduction of acid chlorides to aldehydes with hydrogen and palladium on barium sulfate.[83] It has been found that ferrous ions greatly increase the speed of the reduction of aldehydes when a platinum catalyst is used.[84]

Acetylenic compounds can be reduced to the corresponding ethylenic or paraffin compounds. The latter can also be obtained from ethylene derivatives. It has been noted that when the reduction of a compound containing conjugated unsaturation is interrupted when only one mole of hydrogen has been absorbed, the reaction product is a mixture of saturated compound and starting material.[13]

Aldehydes are most easily reduced through the use of platinum oxide and ferrous ions. The quantities of platinum black which must be used to achieve the same results are very large. If the reduction is not interrupted after one mole of hydrogen has been absorbed, the product is often the corresponding hydrocarbon. Ketones can be reduced to the secondary alcohols or hydrocarbons.

An alcoholic hydroxyl group may be replaced with hydrogen, but does not necessarily interere with the reduction of other groups in the molecule. In special cases the hydroxyl may be replaced without reducing other functional groups present in the molecule.

Nitriles are reduced to primary or secondary amines. The carbon to nitrogen double bond found in anils is usually split with the production of an amine and a hydrocarbon; while that in semicarbazones, hydrazones, and azines is reduced without cleavage. The reduction of oximes usually yields primary or secondary amines, but in some cases hydroxylamine derivatives can be obtained. Nitrones also yield hydroxylamine derivatives on reduction. Nitro compounds yield amines or any of numerous intermediate reduction products depending on the catalyst, solvent, time of reduction, etc. Many examples will be found in the table.

Aromatic rings may be reduced, and alkyl-aryl ethers are often cleaved in the course of such a reaction.[93] Carboxyl groups are not usually attacked; one of the carbonyls in phthalide is reduced. In the preparation of hydroaromatic aldehydes it is necessary to protect the aldehyde group.[28,99]

Heterocyclic oxygen compounds may be reduced so that saturated cyclic or open chain compounds are produced. The reduction of heterocyclic nitrogen compounds usually leads to the formation of the corresponding saturated ring compounds.

In many cases it is possible to remove inert halogen by catalytic hydrogenation. Aryl halides and ω-bromostyrene are examples. The reaction proceeds smoothly with more active halogen. Its use in the preparation of aldehydes from acid chlorides has already been mentioned.

A few specialized reductions will be found listed at the end of the table.

Page numbers in the references ordinarily are for the procedure in question. When the article is short or contains pertinent information, the initial page of the article may be listed.

Preparation of the Catalysts

1. Platinum black is usually prepared according to the method of Loew[1] as modified by Willstätter.[2] In this method, platinous chloride is reduced by formaldehyde in alkaline solution.

2. Palladium black can be prepared (a) from palladous chloride by the method given above for platinum black;[3] (b) by the reduction of palladium ammonium chloride with formic acid in alkaline solution;[4] or (c) by the treatment of palladous chloride with calcium hydride.[5]

The main difficulty in the use of the metal blacks is that the catalytic activity of different samples varies greatly.

Active catalysts can often be prepared using an inert carrier such as charcoal,[6,7] calcium carbonate,[8] barium sulfate,[9,10] or silica gel.[11]

3. Colloidal platinum, stabilized by sodium protalbinate or lysalbinate[12,13,14] or by gum arabic[15] is useful. The first two stabilizers give a preparation which can be used in neutral or alkaline solutions, while the third can be used in neutral, alkaline, or acid solution.

4. Colloidal palladium, stabilized by gum arabic,[15,16] is sometimes used.

A useful procedure introduced by Skita[17] consists in the reduction of the metallic chloride in the presence of gum arabic, the substance to be reduced, and a small amount of colloidal platinum or palladium solution.

5. Platinum oxide, prepared by the fusion of chloroplatinic acid with sodium nitrate, has been found to be a superior catalyst in many cases.[18,19] The active catalyst is a mixture of platinum and platinum oxide resulting from partial reduction of the oxide obtained in the fusion.

6. Palladium oxide has approximately the same activity as does platinum oxide. It is prepared by the fusion of palladous chloride with sodium nitrate.[20]

REDUCTIONS

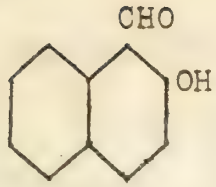
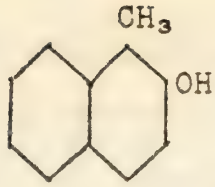
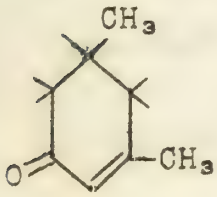
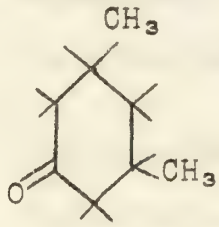
Compound	Catalyst	Product	Yield	Ref.
-C≡C-				
HC≡CH	Pt Black	ethane	70%	21
$C_6H_5C{\equiv}CH$	Coll.Pd	styrene	-	22
		ethylbenzene	-	22
$C_6H_5C{\equiv}CC_6H_5$	Coll.Pd	isostilbene	-	22
		dibenzyl	-	22
$C_6H_5C{\equiv}CCOONa$	Coll.Pd	allocinnamic acid	-	23
		phenylpropionic acid	-	23
$(EtO)_2CHC{\equiv}CCH(OEt)_2$	Coll.Pd	maleinaldehyde acetal	82%	24
$[Me_2C(OH)C{\equiv}]_2$	Coll.Pd	cis-ethylene deriv.	-	25
$(C_6H_5CHC{\equiv})_2$	Pd black	hydrocarbon	100%	26
$[R_2C(OH)C{\equiv}]_2$	Pt black	glycol and tert. alc.	-	26
	Pd black	hydrocarbon	mostly	26

$>C=C<$

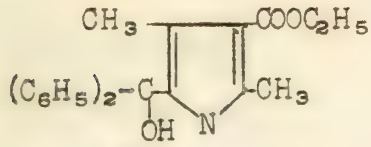
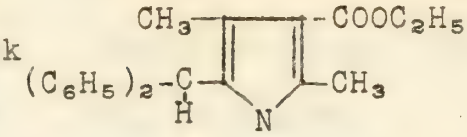
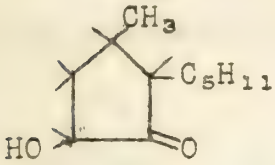
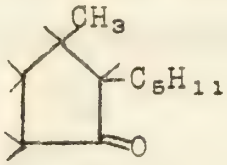
$H_2C=CH_2$	Pt black	ethane	100%	21
	Coll.Pd	ethane	100%	27
$C_6H_5CH=CHCH(OEt)_2$	Pt black	$C_6H_5CH_2CH_2CH(OEt)_2$	88%	28
Phytol ($C_{20}H_{40}O$)	Pt black	$C_{20}H_{42}O$	good	29
Oleic acid (ester)	Pt black	stearic acid (ester)	100%	29
Fumaric acid	Coll.Pd	succinic acid	70%	30
Maleic acid	Coll.Pd	succinic acid	-	30
Cinnamic acid	Coll.Pd	phenylpropionic acid	90%	30
MeOOC  COOMe	Pd black	p-$C_6H_{10}(COOMe)_2$	50%	31
$C_6H_5CH=CHCH=CHCOCH_3$	Coll.Pd (1 mole H_2)	$C_6H_5CH_2CH_2CH_2CH_2COCH_3$	50%	13
$Me_2C=CHCOCH=CMe_2$	Coll.Pd (1 mole H_2)	dihydrophorone	-	13

-CHO

$C_5H_{13}CHO$	Pt oxide	$C_6H_{13}CH_2OH$	90%	19
Glucose	Pt black	d-sorbite d-mannite	-	32
C_6H_5CHO	Pd-$BaSO_4$ (quinoline poison)	$C_6H_5CH_2OH$	75%	33
C_6H_5CHO	Pt oxide	$C_6H_5CH_2OH$	98%	19
$CH_3OC_6H_4CHO$	Pt black	$CH_3OC_6H_4CH_2OH$	90%	34
o-Chlorobenzaldehyde	Pt oxide	o-Chlorobenzyl alc.	-	35
Piperonal	Pd-$BaSO_4$ (1 mole H_2)	alcohol	85%	33
	(2 moles H_2)		90%	33
Vanillin	Pt oxide	alcohol	-	18
Salicylaldehyde	Pt oxide	alcohol	92%	35
	Pt black	o-cresol	-	36

	Pt black		-	36
o-Veratrylaldehyde	Pt black	alcohol	90%	37
Polyhydroxy aromatic aldehydes	Pt oxide	alcohols	poor	35
$C_6H_5CH{=}CHCHO$	Pt oxide	cinnamyl alcohol	95%	38
	Pt black (1 mole H_2)	$C_6H_5CH_2CH_2CHO$ and unsat. alcohol	-	39
	(2 moles H_2)	$C_6H_5CH_2CH_2CH_2OH$	85%	39
$CH_3CH{=}CHCHO$	Pt black	n-butyraldehyde	53%	40
		n-butyl alcohol	21%	
$CH_3CH_2CH{=}C(CH_3)CHO$	Coll.Pd	sat. aldehyde	67%	41
		unsat. alcohol	15%	
$>C{=}O$				
$C_2H_5COCH_3$	Pt oxide	Sec. alcohol	98%	18
$CH_3COCH_2COCH_2$	Pt black	pentane	55%	42
	Pt black(Fe)	alcohol and glycol	55%	42,43
$Me_2C{=}CHCOCH_3$	Coll.Pd	sat. ketone	85%	44
	Pt black	sat. ketone or sat.alc.ad vol.	95%	43
Cyclopentanone	Pt black	alcohol	95%	43
	Coll.Pd		82%	45
ArCOR	Pd-charcoal	alcohol	good	46
	Pt black	alcohol	poor	46
$C_6H_5COCOC_6H_5$	Pt black	benzoin	90%	47
$C_6H_5COCHOHC_6H_5$	Pt black	glycol	90%	47
$C_6H_5COCH_2NH_2$	Pd-charcoal	amino alcohol	98%	48
	Coll.Pd	amino alcohol	98%	48

-OH

$CH_3COC(COOEt)=CHOH$	Coll.Pd	methyl acetoacetic ester	-	49
	Pt black		-	50
	Coll.Pd		60%	51
$C_6H_5CH(OAc)COOMe$	$Pd\text{-}BaSO_4$	phenyl acetic acid	60%	52

(The above is typical for compounds related to benzyl alcohol.)

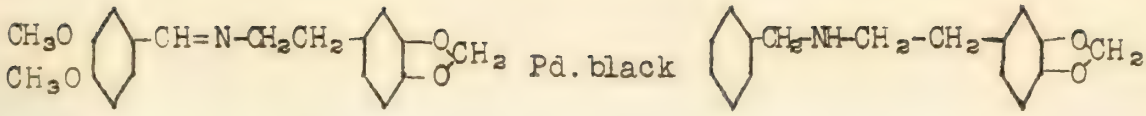
$C_6H_5CH=CHOCOCH_3$	Coll.Pd	$C_6H_5CH_2CH_2OCOCH_3$	82%	17
$C_6H_5C(CH_3)=CHOCOCH_3$	Pt black	$C_6H_5CH(CH_3)CH_2OCOCH_3$	-	53

-C≡N

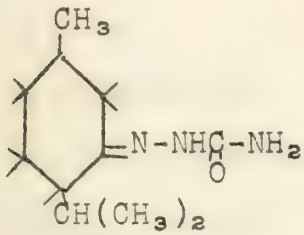
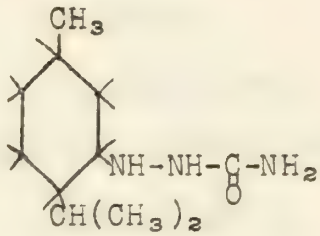
RCN	Pt black [$(R'CO)_2O$] (Pt black alone	RCH_2NHCOR' sec. amine)	63-89%	54
ArCN	Pt black [$(R'CO)_2O$] (Pt black alone	$ArCH_2NHCOR$ sec. amine)	63-89%	54
C_6H_5CN	$Pd\text{-}BaSO_4$	$C_6H_5CH_2NH_2$	80%	55
$C_6H_5CH_2CN$	$Pd\text{-}BaSO_4$ (HCl)	$C_6H_5CH_2CH_2NH_2$	73%	55
o-ClC_6H_4CN	$Pd\text{-}BaSO_4$	o-$ClC_6H_4CH_2NH_2$	60%	55
	$Pd\text{-}BaSO_4$ (NaOAc)	$C_6H_5CH_2NH_2$	85%	55
RCN	Pd-charcoal	RCH_2NH_2	95-100%	56

>C=N-

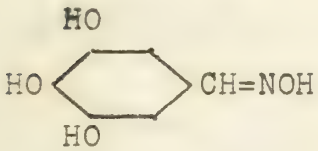
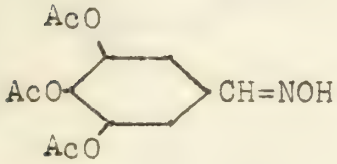
$C_6H_5CH=NC_6H_5$	$Pd\text{-}BaSO_4$	$C_6H_5NH_2$	-	55
$(C_6H_5)_2C=NC_6H_5$	$Pd\text{-}BaSO_4$	$C_6H_5NH_2$ and $C_6H_5CH_2C_6H_5$	100%	55



- 58

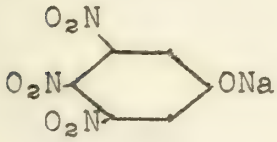
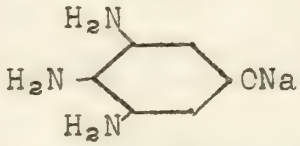
$RCH{=}NNHCONH_2$	Coll.Pt	semicarbazides	80-100%	61
$Me_2C{=}NNHCONH_2$	Coll.Pt	$Me_2CHNHNHCONH_2$	70%	62
$CH_3CH{=}NNHCONH_2$	Pt black	$CH_3CH_2NHNHCONH_2$	-	63
	Coll.Pt		-	62
$CH_3CH{=}NNHC_6H_5$	Coll.Pt	$CH_3CH_2NHNHC_6H_5$	95%	62
$Me_2C{=}NN{=}CMe_2$	Coll.Pt Pt black	$Me_2CHNHNHCHMe_2$ $Me_2CHNHNHCHMe_2$	98% 90%	59 60

<u>$>C{=}NOH$</u>

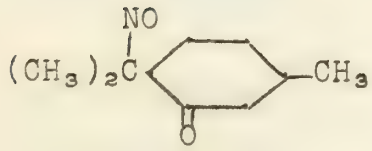
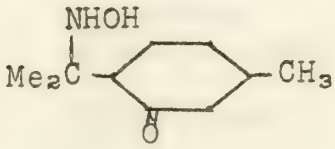
$RCH{=}NOH$	Pd-charcoal	RCH_2NH_2	95-100%	56
$C_6H_5CH{=}NOH$	Coll.Pd	$C_6H_5CH_2NH_2$ and $(C_6H_5CH_2)_2NH$	-	64
HOC_6H_4CHNOH	Pd black	$HOC_6H_4CH_2NH_2$	100%	65
$(C_6H_5)_2C{=}NOH$	Pd-$BaSO_4$	$(C_6H_5)_2CHNH_2$	80%	55
$(C_6H_5)_2C{=}NOAc$	Pd-$BaSO_4$	$(C_6H_5)_2CHNH_2$	89%	55
	Pd-$BaSO_4$	digallylamine	-	57
	Pd-$BaSO_4$	primary amine	75%	57
$ArCOC(R){=}NOH$	Pt black	$ArCHOHC(R)HNH_2$	-	66
$C_6H_5COC(CH_3){=}NOH$	Coll.Pd	$C_6H_5CHOHC(CH_3)HNH_2$	24%	67
$RR'C{=}NOH$	Pt black	$RR'CHNHOH$	good	68

$C_6H_5N(\rightarrow O)=CHC_6H_5$	Pt black	$C_6H_5N(OH)CH_2C_6H_5$	95%	69

$-NO_2$

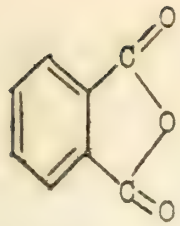
CH_3NO_2	Pd-$BaSO_4$	CH_3NHOH	98%	70
$CH_3CHOHCH_2NO_2$	Pd-$BaSO_4$	$CH_3CHOHCH_2NHOH$	81%	70
$CH_3(CH_2)_5CHOHCH_2NO_2$	Pd-$BaSO_4$	$CH_3(CH_2)_5CHOHCH_2NHOH$	70%	70
$CHNO_2(CH_2OH)_2$	Pd-$BaSO_4$	$CHNH_2(CH_2OH)_2$	93%	71
$C_6H_5CH=CHNO_2$	Pt black	$C_6H_5CHCH_2NO_2$ $C_6H_5CHCH_2NO_2$	17%	72
$C_6H_5CH=CHNO_2$	Pt black (HCl)	$C_6H_5CH_2C=NOH$	-	73
$ArNO_2$	Pt oxide	$ArNH_2$	80-85%	74
$C_6H_5NO_2$	Pd-charcoal	C_6H_5NHOH	80%	75
	Pd-charcoal	$C_6H_5NH_2$	90%	75
	Pd-$CaCO_3$	$C_6H_5N=N(O)C_6H_5$	98%	76
m-$C_6H_4(NO_2)_2$	Pd-charcoal	m-$O_2NC_6H_4NHOH$	--	75
	Pd-charcoal	m-$O_2NC_6H_4NH_2$	-	75
	Pd-NaH_2PO_2	m-$C_6H_4(NH_2)_2$	100%	77
m-$CH_3C_6H_4NO_2$	Pd-$CaCO_3$	(m-$CHC_6H_4N=)_2$	95%	76
p-$CH_3C_6H_4NO_2$	Pd-$CaCO_3$	(p-$CH_3C_6H_4NH-)_2$	92%	76
	Coll.Pd		-	78

NO

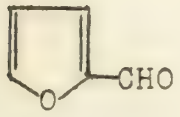
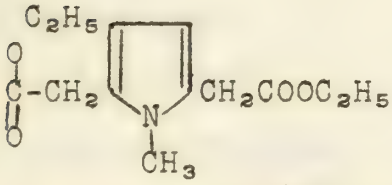
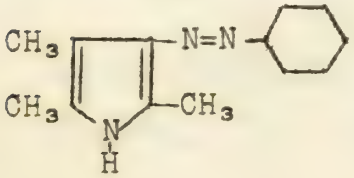
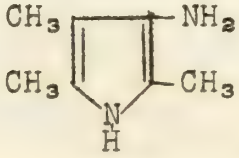
	Pt black		100%	79

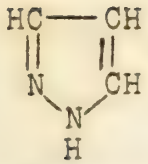
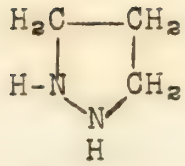
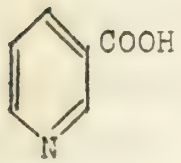
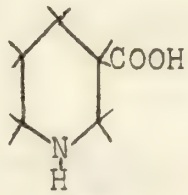
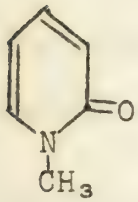
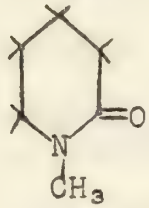
Aromatic rings

C_6H_6	Coll.Pd	C_6H_{12}	-	85
$Me_2C_6H_4$	Pt black	$Me_2C_6H_{10}$	-	86
	Coll.Pt	$Me_2C_6H_{10}$	-	87
$C_{10}H_8$	Pt black	$C_{10}H_{18}$	-	86
C_6H_5OH	Pt black	$C_6H_{11}OH$ and C_6H_{12}	- 40%	86
	Pt oxide	$C_6H_{11}OH$	87%	18
o-$CH_3C_6H_4OH$	Coll.Pt	2-Me-cyclohexanone	80%	88
$C_6H_5NH_2$	Pt black	$C_6H_{11}NH_2$ and $(C_6H_{11})_2NH$	-	86
	Pt oxide	"	-	89
	Coll.Pt (HCl)	$C_6H_{11}NH_2$	97%	90
	Coll.Pt (HOAc)	$(C_6H_{11})_2NH$	95%	90
p-$CH_3C_6H_4NH_2$	Coll.Pt (HCl)	p-$CH_3C_6H_{10}NH_2$	86%	90
o,m,p-$CH_3C_6H_4NHCOCH_3$	Coll.Pt	trans-hydro-aromatic comp.	75-90%	91
	Coll.Pt (HCl)	cis-comp.	75%	91
p-$HOC_6H_4NH_2$	Coll.Pt	$C_6H_{11}NH_2$ and $(C_6H_{11})_2NH$	-	92
p-$C_2H_5OC_6H_4NH_2$	Coll.Pt	$C_6H_{11}NH_2$ nd $(C_6H_{11})_2NH$	-	92
ArOR	Pt black (3 moles H_2)	$C_6H_{11}OR$	-	93
	Pt black (4 moles H_2)	$C_6H_{11}OH$ and RH, or C_6H_{12} and ROH	-	93
C_6H_5COOH	Pt black	$C_6H_{11}COOH$ and $C_6H_5COOCH_2C_6H_5$	68% 32%	94
o-$CH_3C_6H_4COOH$	Coll.Pt	cis-hydro-aromatic comp.	83%	95
p-$CH_3C_6H_4COOH$	Coll.Pt	trans-comp.	-	95
$C_6H_5CH(OH)COOH$	Coll.Pt	hydroaromatic comp.	-	96

	Pt black	hexahydrophthalide hexahydro-o-toluic acid and 6-hexahydrophthalic acid	38% 38% 15%	97 97 97
p-$H_2NC_6H_4COOH$	Pt black	hydroaromatic comp.	95%	98
$C_6H_5CH_2CH(OC_3H_7)_2$	Pt oxide	hydroaromatic comp.	good	28
$C_6H_5CH_2NHC_6H_5$	Coll.Pt	$C_6H_{11}CH_2NHC_6H_{11}$	67%	99
C_6H_5CHO	Coll.Pt Coll.Pt Coll.Pt	$C_6H_5CH_2OH$ $C_6H_5CH_3$ $C_6H_{11}CH_3$	- 80% good	41 41 41
$C_6H_5CH{=}CHCOCH_3$	Pt black	$C_6H_5CH_2CH_2CHOHCH_3$ $C_6H_5CH_2CH_2COCH_3$ $C_6H_{11}CH_2CH_2CHOHCH_3$ all ad vol.	good good good	100 100 100

Heterocyclic rings

	Pt oxide Pd-charcoal Pt oxide	furfuryl alcohol or tetrahydro alc.ad vol tetrahydro alc. pentadiol-1,2 pentadiol-1,5 n-amyl alcohol	100% 95% 98% - - -	101 102 101
	Coll.Pd	tetrahydro comp.	-	103
	Pt oxide	N-methylpyrrolidine	74%	104
	Pt black	tetrahydro comp.	98%	105
	Pt black	 and sulfanilic acid	good 100%	106

	Pd-$BaSO_4$		100%	107
C_5H_5N	Coll.Pt Pt oxide (HCl)	$C_5H_{12}N$	100% -	108 109
Picolines, lutidines and collidines	Coll.Pt	pipecolines, lupetidines and copellidines	60-90%	110
	Coll.Pt		91%	111
	Pt black		100%	112
	Coll.Pt		-	113

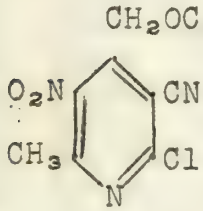
C-X

$CH_2OHCH(Cl)(NO_2)$	Pd-$BaSO_4$	2-nitroethanol	71%	114
$CH_3CH{=}CClCOOH$	Pd-$BaSO_4$	crotonic acid	-	115
$(BrCHCOOH)_2$	Pd-$BaSO_4$	succinic acid	-	115
C_6H_5Br	Coll.Pd	C_6H_6	-	115
p-$O_2NC_6H_4Br$	Pd-$BaSO_4$	$C_6H_5NH_2$	-	115
$C_6H_5CH{=}CHBr$	Coll.Pd	$C_6H_5C_2H_5$	62%	116
$C_6H_5CHBrCHBrC_6H_5$	Pt black	$C_6H_5CH_2CH_2C_6H_5$ $C_6H_5CH_2CH_2C_6H_5$ ad vol.	-	117
$C_6H_5CHClCHClC_6H_5$	Pt black	$C_6H_5CH_2CH_2C_6H_5$ only	-	117
$C_6H_5CHCl_2$	Coll.Pd	$C_6H_5CH_3$ and $(C_6H_5CHCl)_2$	75%	116

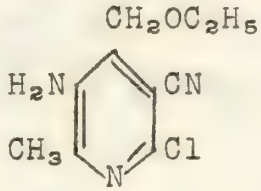
$[(C_6H_5)_2CHCCl_2]_2$	Pd-$CaCO_3$	$[(C_6H_5)_2CHCCl{=}]_2$	-	118
$[(C_6H_5)_2CHCBr_2-]_2$	Pd-$CaCO_3$	$(C_6H_5)_2C{=}C{=}C{=}C(C_6H_5)_2$	-	118
C_3H_7COCl	Pd-$BaSO_4$	C_3H_7CHO	50%	119
C_6H_5COCl	Pd-$BaSO_4$	C_6H_5CHO	97%	119
p-$O_2NC_6H_4COCl$	Pd-kieselguhr	p-$O_2NC_6H_4CHO$	90%	83
p-$CH_3C_6H_4COCl$	Pd-$BaSO_4$ (quinoline)	p-$CH_3C_6H_4CHO$	81%	120
o-$ClC_6H_4CH{=}CHCOCl$	Pd-$BaSO_4$ (quinoline)	o-$ClC_6H_4CH{=}CHCHO$	92%	120

Miscellaneous

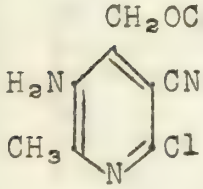
$C_6H_5SO_2Cl$	Pd black	$C_6H_5SO_2H$ $C_6H_5SSC_6H_5$	good 50%	121
$XC_6H_4SO_2Cl$	Pd black	$C_6H_5SO_2H$	50%	121
$C_6H_5CH_2COOC_6H_5$	Pd black	C_6H_5COOH and $C_6H_5CH_3$	95%	122
$[Me_3N(C_6H_5)]Cl$	Pt oxide	C_6H_{12} and Me_3N	62% 100%	89
$C_2H_5OOC_2H_5$	Pt black	C_2H_5OH	-	123



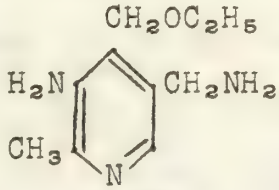
Pt oxide (3 moles H_2)



76% 124



Pt oxide
Pd-charcoal
(3 moles H_2)



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ELECTRONIC THEORY OF REARRANGEMENTS

Whitmore -- Pennsylvania State College
Hauser -- Duke University

For nearly thirty years various workers have realized that the general course of elimination, metathetical, and intramolecular rearrangement reactions could be explained by application of the electronic theory. In 1932, Whitmore formulated a detailed general theory for such reactions on the basis of this concept. He formulated the electronic structure of molecules which undergo rearrangements as

(a) $:\ddot{\underset{\cdot\cdot}{A}}:\ddot{\underset{\cdot\cdot}{B}}:\ddot{\underset{\cdot\cdot}{X}}:$ or (b) $:\ddot{D}::\ddot{A}:\ddot{\underset{\cdot\cdot}{B}}:\ddot{\underset{\cdot\cdot}{X}}:$

where X is any electronegative atom or group. The first step in either case consists in the removal of X with its full complement of eight electrons leaving the atom to which it had been attached with an incomplete valence electron shell or "open sextet." This fragment may then undergo the following changes:

1. Combine with another anion to give a normal product.

(a) $:\ddot{\underset{\cdot\cdot}{A}}:\ddot{\underset{\cdot\cdot}{B}} + :\ddot{\underset{\cdot\cdot}{Y}}: \longrightarrow :\ddot{\underset{\cdot\cdot}{A}}:\ddot{\underset{\cdot\cdot}{B}}:\ddot{\underset{\cdot\cdot}{Y}}:$ or

(b) $:\ddot{D}::\ddot{A}:\ddot{\underset{\cdot\cdot}{B}} + :\ddot{\underset{\cdot\cdot}{Y}}: \longrightarrow :\ddot{\underset{\cdot\cdot}{D}}::\ddot{A}:\ddot{\underset{\cdot\cdot}{B}}:\ddot{\underset{\cdot\cdot}{Y}}:$

2. If there is a hydrogen on atom A, a proton may be lost to give a more unsaturated product.

(a) $:\overset{H}{\ddot{\underset{\cdot\cdot}{A}}}:\ddot{\underset{\cdot\cdot}{B}} \xrightarrow{-H^+} :\ddot{A}::\ddot{B}:$ or

(b) $:\ddot{D}::\overset{H}{\ddot{A}}:\ddot{\underset{\cdot\cdot}{B}} \xrightarrow{-H^+} :\ddot{D}::\ddot{A}::\ddot{B}:$

3. If B has a greater electron affinity than does A, the most readily available pair of electrons from A may shift to B. In system <u>a</u> the shift of the electron pair includes the atom or group attached.

$$R:\ddot{\underset{\cdot\cdot}{A}}:\ddot{\underset{\cdot\cdot}{B}} \longrightarrow \ddot{\underset{\cdot\cdot}{A}}:\ddot{\underset{\cdot\cdot}{B}}:R$$

In the case of <u>b</u> the result is the shift of the double bond:

$$:\ddot{D}::\ddot{A}:\ddot{\underset{\cdot\cdot}{B}} \longrightarrow \ddot{\underset{\cdot\cdot}{D}}:\ddot{A}::\ddot{\underset{\cdot\cdot}{B}}:$$

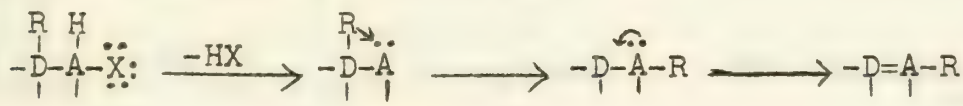
These fragments then may undergo reactions 1 or 2 which, except in the case of <u>2b</u>, give rise to rearranged products. (The bond between A and B may be a double covalent bond as well as a single bond).

Many objections have been raised to the postulation of an intermediate carbonium ion. There is evidence that at least in certain metatheses and in a pinacol type rearrangement an alkyl cation is not actually an intermediate. With the modification, then, that the succeeding reactions above occur simultaneously, Whitmore's generalizations describe the general courses of eliminations, metatheses, and intramolecular rearrangements effected by acids, acidic reagents, and heavy metal salts (all electron acceptors).

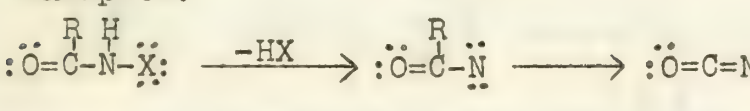
After extensive work by him and his students on the elimination of HX from various types of molecules by bases, Hauser has been able to generally apply the electronic theory in predicting the products of such reactions. It has been demonstrated that these reactions usually are initiated by the attack of the basic reagent upon the hydrogen. Depending, then, upon the solvent, the strength of the base, and the acidic strength of the organic compound, two extreme types of reaction would be Type I, in which the acid-base equilibrium is far on the side of the corresponding salt, and Type II, in which the equilibrium is far on the side of the original acid and base. For both cases, the general course of the reaction may be divided into steps: (1) removal of hydrogen as a proton, (2) elimination of X as an anion, and (3) stabilization of the molecule. For Type I, steps 2 and 3 may be simultaneous while for Type II, all three may be simultaneous and interdependent. Systems in which X is more easily released than a relatively inactive hydrogen may involve the primary removal of X as an anion followed by the loss of a proton. Regardless of the intimate mechanism of the process of elimination, it is the third step, which is after the elements of HX have been removed, that the nature of the products is determined.

The products resulting from the removal of HX from a molecule depends upon the number of atoms involved in the elimination. When HX is removed by a base from the same atom, the molecule may be stabilized by the formation of unsaturated products as follows:

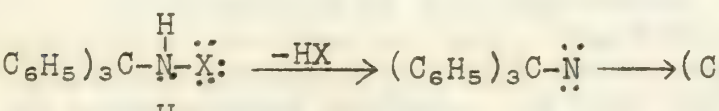
(a) By rearrangement



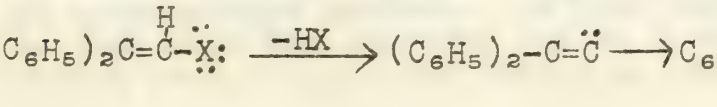
Examples:



(X = halogen, acetate, etc.)

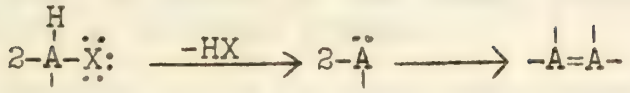


(X = bromine)

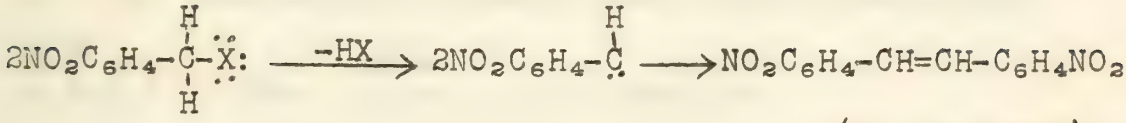


(X = halogen)

(b) By dimerization

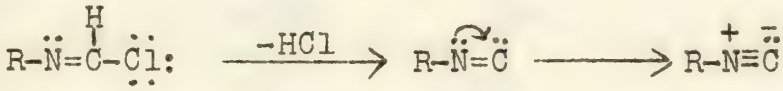


Example:



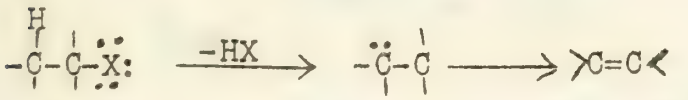
(X = halogen)

A special case of a one-atom system arises when D has an unshared electron pair. The stabilization can then proceed without rearrangement. An example of this situation is found in the formation of isonitriles from primary amines, chloroform, and alkali. The process follows through the intermediate RN=CHCl as follows:

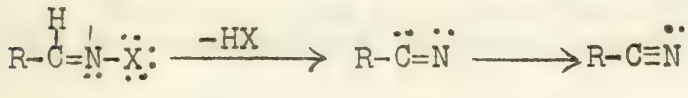


In the two-atom system, the elimination of HX by a base always results in leaving an unshared pair of electrons on the atom next to the one from which X was removed. Hence, an unsaturated product is obtained without rearrangement.

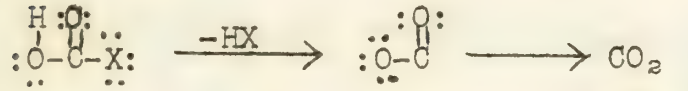
Examples:



(X = halogen)



(X = halogen, acetate, etc.)



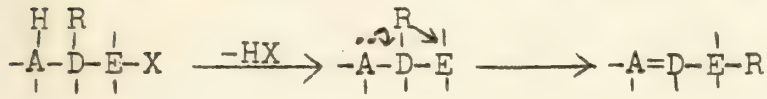
(X = CCl_3)

In compounds of the type A-D-X, HX might be eliminated from a one- or a two-atom system. The former might lead to rearranged or dimerized products as shown above, while the latter would lead to an unrearranged product. In most cases the products are found to be such that the reaction may be considered either as a two-atom system or as a one-atom system in which the hydrogen shifts from

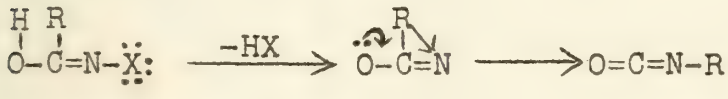
A to D, in both cases yielding an unrearranged product. Cases of rearranged products from this system have been reported, but in the great majority of the cases, products may be predicted by assuming a two-atom system.

Removal of HX by bases from three-atom systems results in the formation of the following products:

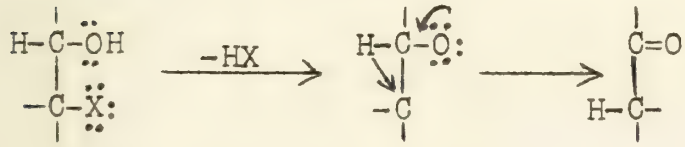
(a) Unsaturated products involving rearrangement:



Examples:

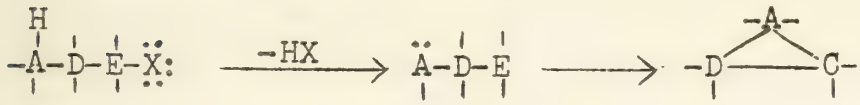


(X = halogen, benzoate, etc.)

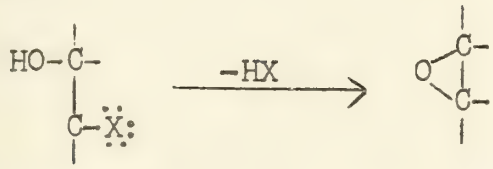


(X = halogen)

(b) Cyclized products:

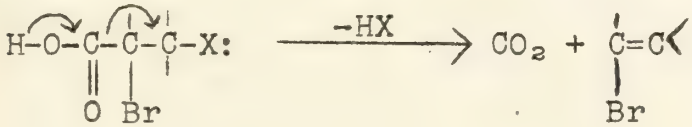


Example:



(X = halogen)

Removal of HX by bases from four-atom systems leads to
(a) two unsaturated products without rearrangement



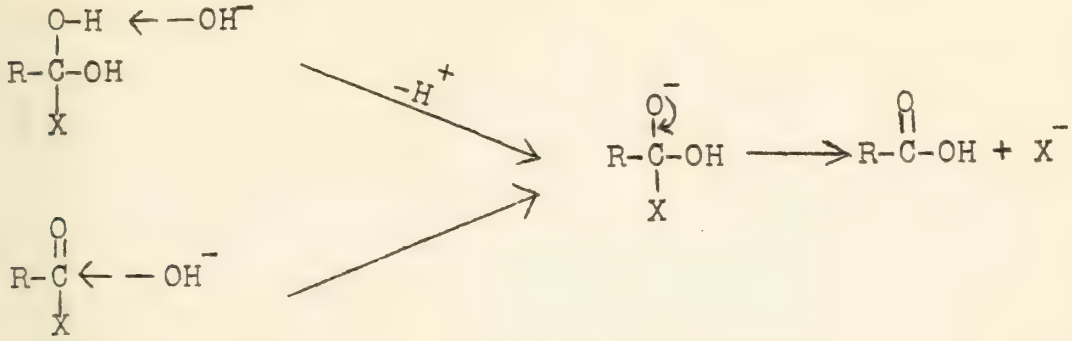
(X = bromine)

(b) Cyclization

Elimination of HX from five- or six-atom systems leads to cyclization.

The reaction of bases with negatively substituted carbonyl

compounds may be considered as involving the elimination of X ($X = OC_2H_5$, NH_2, OCOR, Cl, CCl_3, etc.) from the negative ion formed either by the removal of a proton from the hydrate of the carbonyl or by the direct attack of the hydroxyl ion upon the carbonyl:



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Reported by A. A. Albert